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ORIGINAL ARTICLES

THE ETIOLOGY OF COMMON RESPIRATORY INFECTIONS IN A CIVILIAN ADULT POPULATION*

By Hans G. Grieble, M.D.
INSTRUCTOR IN MEDICINE

George Gee Jackson, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

Harry F. Dowling, M.D.
PROFESSOR OF MEDICINE

WITH THE ASSISTANCE OF

Delores H. Seketa, B.S.
RESEARCH ASSISTANT IN MEDICINE

AND

Truman O. Anderson, Ph.D.
RESEARCH ASSOCIATE IN MEDICINE

(From the Research and Educational Hospitals and the Department of Medicine, University of Illinois College of Medicine, Chicago, Illinois)

The specific etiology of many common acute respiratory illnesses is unknown, but several bacterial and viral agents have been identified as the causes of these illnesses. Through the use of tissue cultures the family of adenoviruses recently has been identified (Enders *et al.*[17], Hilleman and Werner[24], and Rowe *et al.*[49]). Evidence has accumulated that they are responsible for a large number of respiratory infections among military recruits (Berge *et al.*[5], Dascomb and Hilleman[12], Dingle *et al.*[16], Ginsberg *et al.*[19], Hilleman *et al.*[25], Huebner *et al.*[29], Rowe *et al.*[50,51], Seal[52], Van der Veen and Kok[58], and Woolridge *et al.*[60]). In civilian groups, isolated outbreaks of nonbacterial exudative pharyngitis and pharyngoconjunctival fever have been caused by adenoviruses and serologic testing has indicated past infections in

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a high percentage of persons (Bell *et al.*[4], Ginsberg *et al.*[20], Glander *et al.*[21], Huebner *et al.*[29], Jawetz *et al.*[32], Jordan *et al.*[35,36], Kindall *et al.*[38], Parrott *et al.*[42], Sobel *et al.*[55], and Van Horne *et al.*[59]). The prevalence and character of these infections as a cause of common respiratory illnesses in the general population is of interest and has application with regard to the desirability of immunization with an adenovirus vaccine.

There are other specific causes of minor respiratory infections which require laboratory tests that are not always available or practical for the diagnosis of common respiratory diseases. The purpose of the present study was to add tissue culture techniques to other laboratory procedures of previously established value to determine the proportion of common respiratory illnesses among civilian adults that were associated with any of the known or detectable bacterial or viral agents. In the case of diseases where the etiology is still unknown and laboratory tests are unavailable, an evaluation was made of certain clinical criteria as a basis for the differentiation of acute respiratory illnesses.

Material and Methods. A group of 122 adults with acute respiratory infections were studied between August, 1955, and May, 1956. Sixty-two were men and 60 were women. Their ages ranged from 18 to 56 with four-fifths of them in the third or fourth decade of life. The group represented approximately one-fourth of those patients with respiratory infections who voluntarily sought medical care at the Health Service of the Chicago Professional Colleges of the University of Illinois. The only selection of patients was their willingness to come to a special study unit upon referral.* However, patients with an illness of more than 5 days were not admitted to the study.

The pertinent clinical history was supplemented with a standard questionnaire in which the patient recorded the presence and severity of certain symptoms. All subjects were examined and abnormalities of the eyes, nose and throat were graded quantitatively. The oral temperature was recorded at least twice during the course of each illness. The patients were classified as febrile only if an oral temperature reading of more than 100° F. was present. Chest roentgenograms were obtained on all febrile subjects. Following the patient's first visit an initial clinical diagnosis was made on the basis of symptoms and signs. The diagnosis of the illness was classified according to certain previously determined differential criteria which are summarized in Table 1.

All but 2 patients were followed as outpatients. The clinical evaluation and sampling of specimens were performed by the same examiner throughout the study. Specimens for bacteriologic cultures were obtained by swabbing the lower nasal turbinates and septum or tonsils, pillars and posterior pharyngeal wall. The swabs were immersed in 1 ml. of sterile broth and processed for determinative bacteriology within 30 to 60 minutes. The specimens for virus isolation were obtained in the same manner and stored at −70° C. until virus isolation on HeLa cell tissue cultures was attempted. Specimens from the conjunctiva were obtained for bacteriologic and virologic studies in all cases with conjunctivitis. Smears for spirochetes and fusiform bacilli were taken from all cases with vesiculo-ulcerative stomatitis. Blood samples were drawn on the majority of subjects within the first 5 days and again in the second or third week of their illness. The sera were stored at −20° C. until used for serologic tests.

BACTERIOLOGIC METHODS.† Fresh human blood agar pour plates were used to identify beta-hemolytic streptococci. Isolates were grouped serologically. Anti-streptolysin-O antibody titers were determined by the method of Rantz and Randall[45] on 41 pairs of sera including all cases with a positive culture for beta-hemolytic streptococci and on 80% of persons with a febrile illness.

The paired sera were tested simultaneously, and a titer increase of two dilutions or more between the serum collected in the acute and

*The cooperation of Dr. Buford Hall, Director, and the professional staff of the Health Service is acknowledged with appreciation.

†The assistance of Miss Mary Turner and the staff of the clinical bacteriology laboratory is gratefully acknowledged.

TABLE 1.—CRITERIA FOR CLINICAL DIFFERENTIATION OF COMMON ACUTF RESPIRATORY ILLNESSES IN ADULTS

Afebrile Acute Coryza (Common Cold)[1,8,9,31,40]
- Main Criteria:
  - Coryza predominant: rhinorrhea and nasal congestion
  - No fever: temperature less than 100° F.
- Adjunct Syndrome:
  - Pharyngitis: subjective and transient
  - Laryngitis and cough

Undifferentiated Upper Respiratory Infection[8,9,31]
- Main Criteria:
  - Pharyngitis predominant: no exudate, vesicles, or ulcers
  - Laryngitis or bronchitis: hoarseness or cough
  - No fever: temperature less than 100° F.
- Adjunct Syndrome:
  - Coryza: absent or minimal
  - Mild constitutional symptoms

Febrile Acute Respiratory Disease (A.R.D.)[8,9,16,20,56]
- Main Criteria:
  - Fever: temperature greater than 100° F.
  - Pharyngitis: dysphagia, slight redness, follicular lymphoid hypertrophy no exudate, vesicles, or ulcers
  - Laryngitis or bronchitis: substernal burning and cough
  - Constitutional symptoms
- Adjunct Syndrome:
  - Coryza: mild
  - Cervical lymphadenopathy: nontender
  - Atypical pneumonia

Pharyngoconjunctivitis[4,30,35,42]
- Main Criteria:
  - Conjunctivitis: follicular hyperplasia, monocular or binocular
  - Pharyngitis: inflammatory or noninflammatory, exudative or nonexudative
- Adjunct Syndrome:
  - Fever
  - Coryza
  - Constitutional symptoms

Influenza[48,56]
- Main Criteria:
  - Fever: usually high
  - Constitutional symptoms: generalized aching
- Adjunct Syndrome:
  - Nasopharyngitis
  - Bronchitis: pain and cough

Streptococcal Pharyngitis (Adults)[46,53,54,97]
- Main Criteria:
  - Pharyngitis: dysphagia, inflamed throat, tonsillar exudate
  - Cervical lymphadenopathy: diffuse and tender
- Adjunct Syndrome:
  - Fever
  - Coryza and nasal obstruction
  - Leukocytosis: greater than 12,000/c.mm.
  - Otitis media

Nonbacterial Exudative Pharyngitis[9,46,47,53,54]
- Main Criterion:
  - Exudative pharyngitis: slight dysphagia, mild inflammation with lymphoid hypertrophy and pharyngeal exudate
- Adjunct Syndrome:
  - Fever
  - Cervical lymphadenopathy
  - No leukocytosis: less than 12,000/c.mm.

Vesiculo-Ulcerative Pharyngitis
- Main Criteria for:
  - Herpangina[30]: small vesicles or shallow ulcers, or both, with red areola on soft palate and posterior pharynx
  - Herpes simplex[14,48]: clear vesicles on anterior buccal mucosa, lips or tongue
  - Infectious mononucleosis (Pharyngeal syndrome)[27,28]: palatine petechiae, ulcerations or pseudomembranes
  - Vincent's angina[41,48]: superficial ulcerations of the mouth, pseudomembranes, positive smear

recovery phases of the illness was considered significant.

Pneumococci, *H. influenzae, Klebsiella pneumoniae* and *M. pyogenes* var. *aureus* were identified on appropriate media. In the analysis the latter was considered only if isolated from both the nose and throat.

VIROLOGIC METHODS. HeLa cell tissue cultures were inoculated with 0.25 ml. aliquots of the original specimen for the isolation of adenoviruses. Observations for specific cytopathogenicity were continued for at least 7 days and through three serial sub-passages or an average of 25 tubes per original specimen.

Neutralization tests were performed in HeLa cell cultures using 100 to 1000 TC_{50} doses of adenovirus and serial twofold dilutions of serum. The absence of cytopathogenicity for at least 48 hours after complete degeneration of the infected control cell cultures was considered neutralization.

SEROLOGIC METHODS. A pool of adenoviruses of type 2, 3, and 6 was used as antigen in the complement fixation test by the modified method of Kolmer[14]. Inactivated sera were tested in serial twofold dilutions with two units of antigen and complement. Only complete or nearly complete complement fixation was considered positive.

One hundred four acute and 78 recovery phase sera were tested for cold agglutinins. Five hundredths of a milliliter of freshly drawn blood was suspended in 0.5 ml. phosphate buffered saline at pH 7.4. The mixture was incubated at 4° C. for 16 to 18 hours and observed for hemagglutination.

A total of 74 recovery phase sera were tested for heterophile agglutinins for sheep erythrocytes (Paul-Bunnel test for infectious mononucleosis). All those with titers of 1:28 or higher were studied by differential absorption tests as described by Davidsohn *et al.*[13]. The acute and recovery phase sera of 2 persons were retitered simultaneously to demonstrate a rise in titer.

Hemagglutination-inhibition antibody titers against Influenza A prime and B were determined on 65 pairs of sera; 68 paired sera were tested against influenza A (Asian) and C. Recently isolated strains of influenza virus were kindly furnished by Dr. Murray Friedman, Naval Medical Research Unit No. 4, U.S. Naval Training Center, Great Lakes, Illinois. They were designated "A prime 1148," "GL-1760-54B" and "GL-1167-54C." The strain of Influenza A Japan/305/57 virus was received from Dr. Keith Jensen, USPHS. Hemagglutination of a 0.5% suspension of fresh chicken erythrocytes was determined by the Salk pattern test[14]. The method employed was a slight modification of that described by Jordan *et al.*[37]. Receptor destroying enzyme (R.D.E.) of a vibrio cholerae culture was substituted in the case of the Asian A strain by 1/90 molar potassium periodate. Acute and recovery phase sera were tested simultaneously. A fourfold or higher rise in titer was considered significant if reproduced in a repeated test procedure.

Prior to titration for Influenza C antibody by hemagglutination-inhibition it was found necessary to remove cold agglutinins for chick red blood cells by a preliminary absorption. One volume of serum was mixed with four volumes of 10% washed chicken erythrocytes and incubated at 1° C. for 2 hours. The cells were removed by centrifugation, a measured aliquot of the supernatant was removed, mixed with an equal volume of crude RDE and incubated at 37° C. for 16 to 18 hours. The RDE was inactivated at 62° C. for 30 minutes. Twofold serial dilutions of serum were made and four hemagglutinin units of active C virus in 0.25 ml. added.

After incubation for a minimum of 10 minutes at 37° C., washed chick red blood cells, 0.5%, were added and the mixture incubated at 1° C. Hemagglutination was observed after 2 hours and rechecked after 16 to 18 hours.

Results. The frequency of the clinical syndromes encountered is shown in Fig. 1. Acute afebrile coryza was the most common single entity and accounted for more than 35% of the total illnesses. Afebrile upper respiratory infections, which consisted primarily of acute nonexudative pharyngitis, made up nearly one-quarter of the illnesses. Acute febrile respiratory disease was present in 15% and exudative pharyngitis also was present in approximately 15% of the cases. Of the latter group streptococci were suspected as the cause in about one-third. Vesiculo-ulcerative pharyngitis and pleurodynia suggested Coxsackie infections in 6 patients or 5%. Five persons suffered from acute conjunctivitis, usually monocular, as a part of the respiratory illness. The remaining 3 patients had clinical diagnoses of influenza, atypical pneumonia, and non-

suppurative pharyngitis with thyroiditis.

Figure 2 shows the considered diagnosis when all of the laboratory tests were completed upon the 71 patients with afebrile coryza or pharyngitis. The clinical diagnosis was unchanged for almost 90% of the group. Two patients had streptococcal infections, 3 had influenza, 2 had adenovirus infection and one had infectious mononucleosis. Bacterial species that are considered potentially pathogenic for man were isolated from 9 (12%) of these patients. They showed no evidence of bacterial infection, and thus the isolation of these species was considered to represent a carrier state.

A similar analysis of patients with the clinical diagnosis of nonbacterial febrile acute respiratory disease (ARD) or pharyngoconjunctivitis was made (Fig. 3). These syndromes which are characteristic of adenovirus infection were found to be caused by adenoviruses in only 2 of the 23 cases. A type 2 virus was isolated from the conjunctiva and throat of one patient. The other case developed neutralizing antibody for type 3 adenovirus. Influenza was demonstrated in 4 cases of the syndrome and was the most common single cause detected. One patient had serological findings compatible with infectious mononucleosis. The carrier rate for pathogenic bacteria other than hemolytic streptococci was higher among the persons in this group, 30%, than among those with afebrile illnesses, 13%, and in one instance pneumococci may well have caused the disease. The etiology was unknown in two-thirds of the cases.

The combined clinical and laboratory

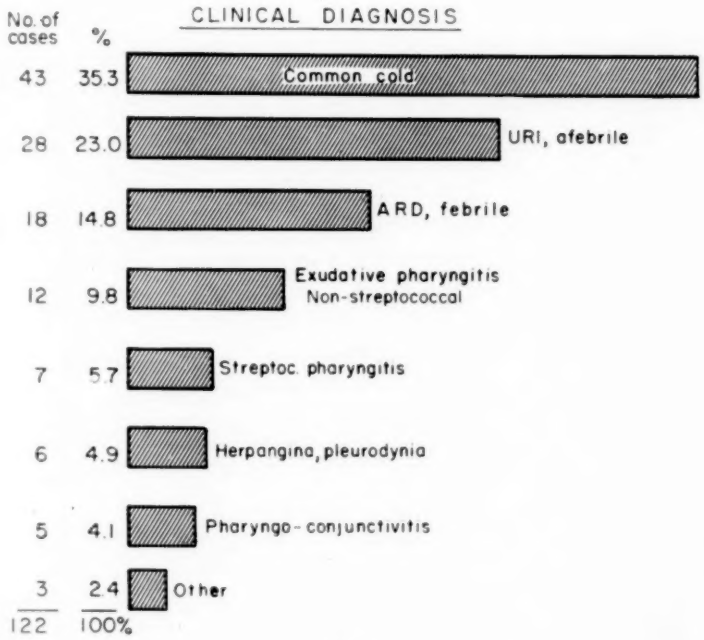

Fig. 1

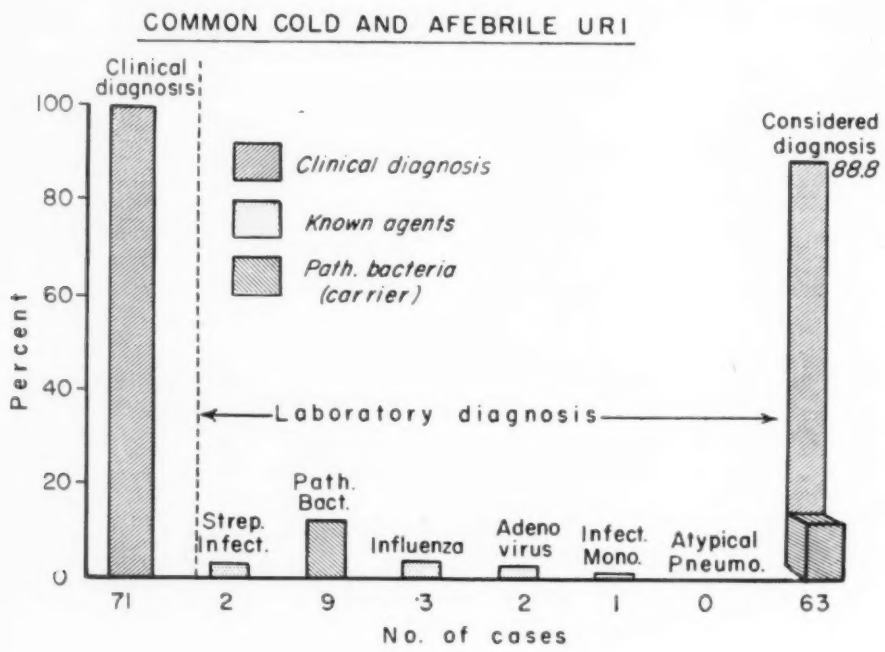
COMMON COLD AND AFEBRILE URI
Clinical diagnosis
Considered diagnosis
88.8
Clinical diagnosis
Known agents
Path. bacteria (carrier)
Laboratory diagnosis
Percent
100
80
60
40
20
0
Strep. Infect.
Path. Bact.
Influenza
Adeno virus
Infect. Mono.
Atypical Pneumo.
71
2
9
3
2
1
0
63
No. of cases

Fig. 2

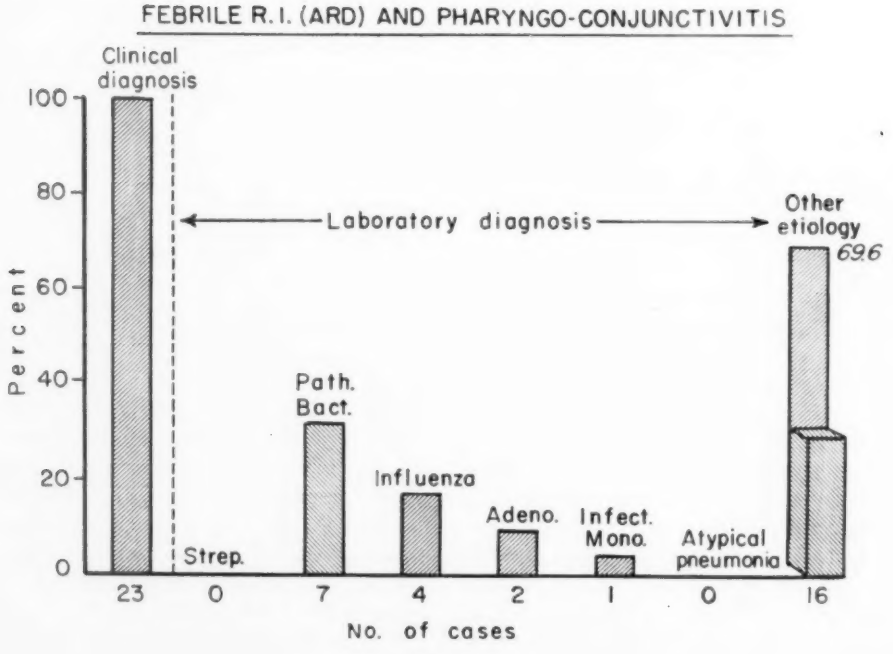
FEBRILE R.I. (ARD) AND PHARYNGO-CONJUNCTIVITIS
Clinical diagnosis
Laboratory diagnosis
Other etiology
69.6
Percent
100
80
60
40
20
0
Path. Bact.
Influenza
Adeno.
Infect. Mono.
Atypical pneumonia
Strep.
23
0
7
4
2
1
0
16
No. of cases

Fig. 3

data on patients with exudative pharyngitis are shown in Fig. 4. Among the 12 persons who were clinically diagnosed as nonbacterial pharyngitis, no viral infections of the kinds under investigation were identified and only one patient had a streptococcal infection. The carrier rate for other pathogenic bacteria was 25%. The data indicate that more than 90% of cases detected. Potentially pathogenic bacteria other than streptococci were isolated from the throats of 2 persons.

The diagnoses for the entire group of illnesses as they were revised when the clinical and laboratory data were considered together are shown in Fig. 5. Afebrile coryza and pharyngitis of unknown etiology accounted for 52% of the illnesses.

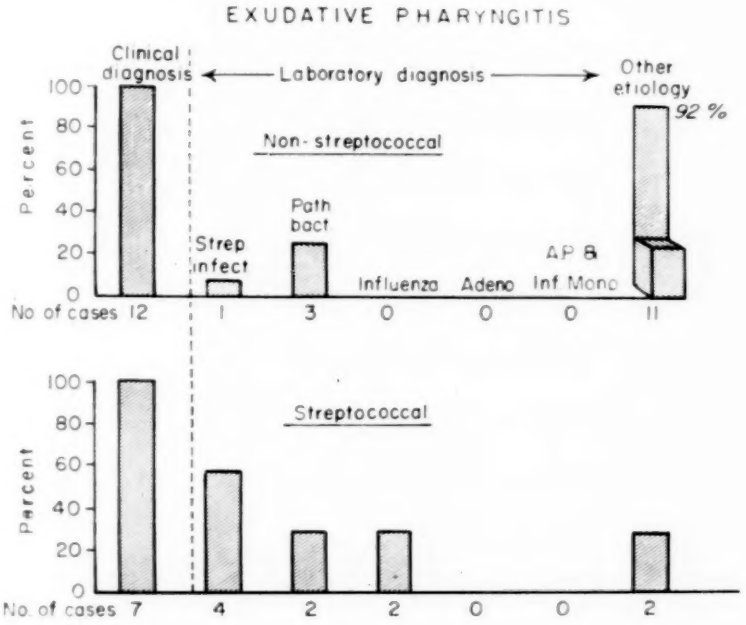

Fig. 4

in this clinical category must be considered of unknown etiology.

A clinical diagnosis of streptococcal pharyngitis was made for 7 patients shown in the lower panel of Fig. 4. Streptococcal infection was substantiated by laboratory data in 4 of the 7 cases. One of these patients had a double infection with Influenza B virus and beta-hemolytic streptococci. He is shown under each heading in the graph. One other patient also had influenza but dual infection was not

Acute nonbacterial febrile respiratory disease including influenza and adenovirus infections accounted for 20% of the illnesses. Influenza infections in 10 patients comprised 8.2% of all illnesses, 15.2% of the paired sera tested, and more than one-fourth of those tested from the group with febrile acute respiratory infections without exudative pharyngeal inflammation. Infections with A prime, B and C viruses were of equal numerical importance. Evidence for infection with

one of the adenovirus agents was found in only 4 patients or 3.3%. Thus, the adenoviruses caused febrile infections rarely whereas influenza (A, B, and C) was a prominent cause of the syndrome even during a nonepidemic season. Two syndromes characteristic of Coxsackie virus infection, herpangina and pleurodynia, were present in 5%.

only 3 of 16 verified cases, or 19%. Influenza was suspected only once and confirmed as an Influenza B infection. Clinically the other 9 patients with the final diagnosis of influenza had presented as common colds: 2 (A prime and C), afebrile U.R.I.; 1 (A prime), febrile A.R.D.; 3 (A prime, B and C), exudative pharyngitis; 1 (C) and strep-

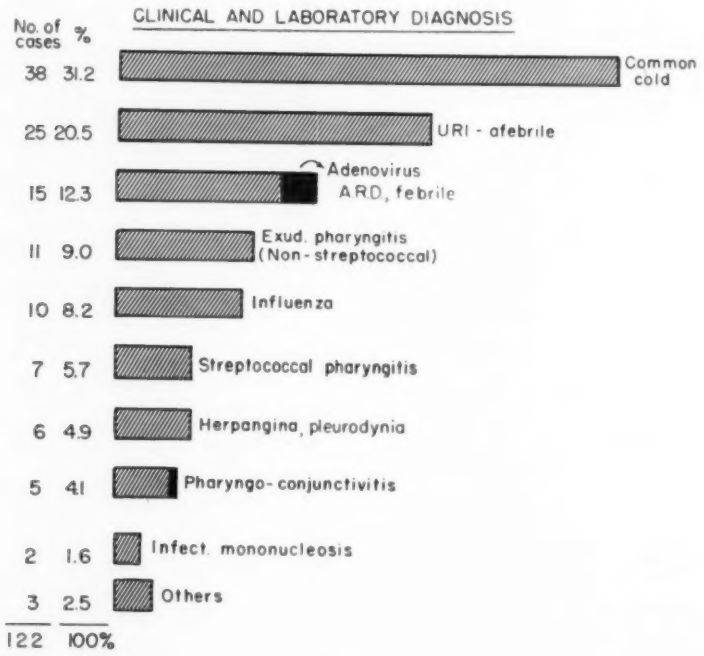

Fig. 5

Streptococcal pharyngitis was found in 6% of the entire group. Pharyngitis with conjunctivitis was found in 4%. Two cases of infectious mononucleosis were serologically established and the clinical diagnosis in the remaining 3 patients was unchanged. No illness was encountered, which was associated with cold agglutinins at a titer of 1:20 or higher.

The proper clinical diagnosis of a specific viral infection was made in

tococcal pharyngitis in the case of one patient with a dual infection. The clinical features of the adenovirus infections led to the initial diagnoses of common cold, afebrile U.R.I., pharyngoconjunctivitis and A.R.D. The latter 2 are characteristic syndromes of adenovirus infection but the patient with pharyngoconjunctivitis had no fever nor hyperplastic follicular conjunctivitis. Infectious mononucleosis was not suspected in one patient with

afebrile acute coryza nor one with febrile acute respiratory disease. Only one of the roentgenographic minifilms of the chest showed pneumonia. This patient was clinically classified as atypical pneumonia of unknown cause.

The serological status of the patients in the entire group who were studied with regard to influenza and adenovirus infections is shown in Table 2. Influenza C, adenovirus, Influenza B, and Influenza A prime respectively, was the order of frequency of positive reactions. Nearly two-thirds of the subjects showed evidence of prior infection with at least one of these agents.

TABLE 2.—ANTIBODIES IN THE INITIAL SERA FROM CIVILIAN HOSPITAL TECHNICAL, CLERICAL AND PROFESSIONAL PERSONNEL WITH ACUTE RESPIRATORY INFECTIONS (1956)

	Influenza				*Adenovirus*	
	A	*A-Prime*	*B*	*C*	*Pooled Antigen*	*C.F.*
HI Test Titer	*Asian*	*G.L. 1148*	*G.L. 1760*	*G.L. 1167*	*Types 2, 3, 6*	*Test Titer*
	No. Positive				*No. Positive*	
<10	62	37	27		23	8
<20				23		
10	1	10	13		12	8
20	1	6	10	21	15	16
40	3	8	8	12	9	32
80	—	3	5	6	2	64
160	—	—	2	3	—	—
320+	—	1	—	3	—	—
Total No.	68	65	65	68	61	
Total Pos.	5	28	38	45	38	
% Pos.	7	43	59	66	62	

At the time of the first visit to the clinic some species of potentially pathogenic bacteria were recovered from the noses and throats of 17 out of 106 persons or 16% of those without beta-hemolytic streptococci and who had received no antibiotic or sulfonamide therapy. Pneumococci were encountered in 10 instances, *Hemophilus influenzae* in 3, *Klebsiella pneumoniae* and strains of *Micrococcus pyogenes* var. *aureus*, coagulase-positive, in 2 cases each. A second nose and throat culture from 31 patients with obviously negative cultures who received no antibacterial therapy was obtained one week after the first visit. Six persons who had a common cold, U.R.I. or A.R.D. yielded bacterial species listed among the potential pathogens, a conversion rate of 19%. Thus, altogether at least 26% of patients in this series harbored one of these bacterial species in their respiratory passages sometime during the course of their illness.

Discussion. The addition of tissue culture techniques using a human epithelial cell line, strain HeLa, to the study of common respiratory infections was made to test for adenoviruses as a cause of such illnesses. A variety of clinical syndromes followed infection with adenoviruses. These include acute febrile pharyngitis (A.R.D.) with and without pneumonia (Berge *et al.*[5], Dascomb and Hilleman[12], Dingle *et al.*[16], Ginsberg *et al.*[19], Hilleman *et al.*[25], Kindall *et al.*[38], and Woolridge *et al.*[60]), pharyngoconjunctival fever (Bell *et*

al.[4], Cockburn[7], and Parrott *et al.*[42]), nonstreptococcal exudative pharyngitis (Dascomb and Hilleman[12], Ginsberg *et al.*[20], Huebner *et al.*[29], and Jordan *et al.*[35]), an influenza-like illness (Commission[8], Dascomb and Hilleman[12] and Stuart-Harris *et al.*[56]), afebrile nasopharyngitis (Hilleman *et al.*[26], and Rivers[48]), and keratoconjunctivitis (Jawetz *et al.*[32,33]). However, approximately one-half of the infections among adults produce no symptoms (Hilleman *et al.*[25]). The different immunologic types of virus cause illness with a considerable overlap in symptoms, but also with some general differences. Types 3, 4, and 7 have been the principal cause of infections among adults in the United States. There has been a marked and consistent discrepancy in the frequency of types of adenoviruses in military and civilian populations. Previous studies have shown that 30 to 90% of febrile respiratory infections and 5 to 30% of afebrile respiratory illnesses among military personnel were caused by types 4 and 7 adenovirus.

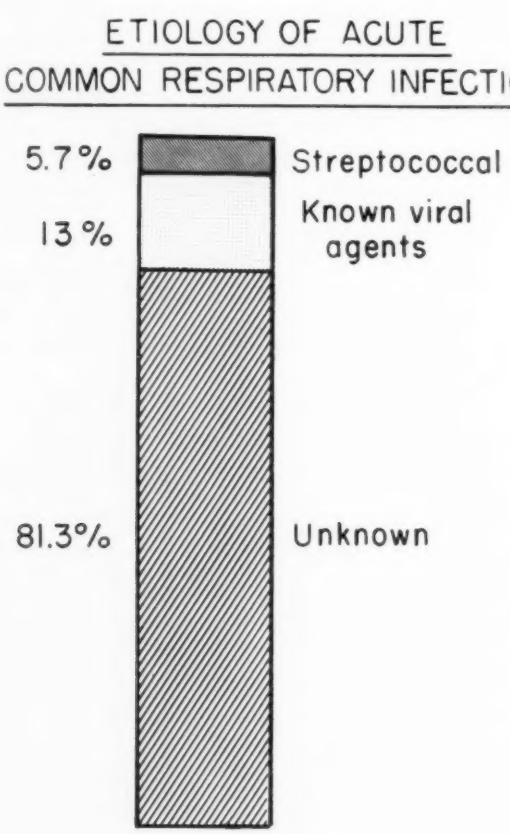

Fig. 6

The present investigation has shown the minor importance of adenoviruses as a cause of common respiratory infections among civilian adults. Other

studies of civilian populations have consistently shown that only 2 to 5% of febrile respiratory infections and very few afebrile infections are caused by adenoviruses (Balducci *et al*[2], Evans[18], Grist *et al.*[23], Jordan *et al.*[35,36], and Price[43]). These are predominantly caused by type 3 and in contrast to the military experience, infection with type 4 virus is rare. Types 1, 2, 5, 6, and 10 produce respiratory illness, conjunctivitis, and a grippe-like syndrome. Among our patients a type 2 strain caused pharyngoconjunctivitis, 2 patients developed increased antibodies for type 3 and one patient had a rise in complement-fixing antibody only. Three of these patients were afebrile. Thus, among all the cases diagnosed by clinical and laboratory observation as A.R.D., nonbacterial exudative pharyngitis and pharyngoconjunctivitis, the three syndromes most characteristic of infection with adenovirus, only 16% had evidence of such an infection. The cause of these illnesses among civilians is unknown in 84% of cases. The data suggest that immunization with adenovirus vaccine would have little effect in reducing total respiratory illnesses. The mild nature of the recognized infections also makes immunization of doubtful need or benefit.

Influenza was the most frequent viral infection identified in these studies. The cases represented nonepidemic influenza and various serologic strains were present. The infections were not diagnosed clinically with any greater accuracy than chance. In retrospect the systemic manifestations were no greater than expected with A.R.D., and in the absence of an epidemic influenza cannot be easily differentiated among the causes of nonbacterial febrile respiratory illnesses.

Identification of the Coxsackie viruses among the patients with clinical herpangina was not attempted. The pharyngeal lesions and symptoms were characteristic of proven cases reported in the literature (Huebner *et al.*[30]). It is quite unlikely that this represents any greater accuracy as one etiologic diagnosis than the 20% observed for other viral infections, and this group of patients should probably be considered on a descriptive basis as vesiculo-ulcerative pharyngitis of perhaps diverse causes.

The hope that the use of tissue cultures of one or two cell lines and additional serologic tests for detectable viral agents would materially reduce the number of undiagnosable common respiratory infections among civilians was not realized. The further hope that an effective vaccine against one of these agents would substantially reduce the total amount of acute respiratory disease also is unsupported. Considering all of the foregoing viral agents for which tests were available, they accounted for a total of 19% of the illnesses. In a recent report Evans[18] came to a similar conclusion. There are other known viruses: poliomyelitis, myxovirus parotidis (mumps), measles, herpes simplex, ornithosis and Coxiella burnetii, which may cause minor respiratory infections (Am. Pub. Health Assn.[14], and Rivers[48]). Newcastle virus may be a rare cause of human conjunctivitis (Burnet[6], and Quinn *et al.*[44]) and the disease-producing role of the increasing number of ECHO viruses is uncertain[10,14]. However, it is likely that all of these additional viruses together cause less than 5% of common respiratory illnesses except in epidemics.

Throughout these studies the isolation of one of the pathogenic agents and a significant increase in the antibody titer for that agent in the person's serum have been considered evidence of infection. In most instances only the latter criterion was available. The

temporal relationship of the infection to the clinical symptoms has in turn been considered indicative of cause and effect. In most cases this is probably true, but there is little doubt that in some of the cases these agents are commensals. On the other hand, the techniques used for the isolation of specific bacteria and viruses and for the serologic demonstration of antibody response in the patient are inadequate unequivocally to identify every case of infection with one of the particular agents under study.

Acute afebrile coryza (the common cold) and afebrile undifferentiated upper respiratory infections were rarely caused by any of the presently known microbial or viral agents. These two clinical syndromes accounted for the majority of the illnesses. These findings support the evidence from studies on volunteers for considering them as nosologic entities (Andrewes[1], Commission[8,9], and Lovelock *et al.*[40]). Our own studies on volunteers[31] suggest that the clinical syndromes of the common cold with rhinorrhea, and undifferentiated respiratory infections with pharyngitis are due to the specific properties of unknown transmissable infectious agents rather than to the reaction of the individual host elicited by a single agent.

The occurrence of beta-hemolytic streptococcal infections in about 6% of persons is comparable to some other studies upon family groups and outpatients (Dingle *et al*[15] and Rantz[47]). Among adults the accurate clinical diagnosis of streptococcal pharyngitis has been reported possible in 65 to 80% of the cases (Seal *et al.*[53,54]). Four of the 7 patients with bacteriologic and serologic evidence of streptococcal infection in this series were recognized clinically. One of them was a double infection with a virus, a situation which has been encountered with variable frequency in influenza epidemics (Gosharian *et al.*[22], and Kilbourne and Loge[39]).

The role of bacteria that are potentially pathogenic for humans such as pneumococci, *Klebsiella pneumoniae*, *Hemophilus influenzae* and *Micrococcus pyogenes* var. *aureus*, coagulase-positive, in nonpneumonic respiratory infections is not entirely clear. In some instances they may represent a causative relationship, but subjects with non-streptococcal exudative pharyngitis did not harbor these organisms more frequently than others without exudative inflammation. On the other hand, these bacterial species were significantly more frequent among the patients with nonspecific febrile respiratory infection or pharyngoconjunctivitis than among patients with a common cold or afebrile undifferentiated respiratory infection. Throat cultures were positive for one of these species of organism in 17% of the subjects studied, which is within the expected carrier rate among non-diseased individuals (Topley and Wilson[57]). The isolation of one of these strains from the cultures of an additional 19% of the subjects restudied during the second week of illness might represent only a transient carrier state but it is commonly considered an opportunistic superinfection. Whatever the mechanisms involved, controlled studies concerning the effect of antibiotic therapy on the incidence and course of common viral respiratory infections suggest that these organisms have no consistent influence on the general course of these infections and antibiotic prophylaxis is of doubtful benefit. (Cronk *et al.*[11] and Jones, Bigham and Manning[34]).

Clinical diagnosis of the common respiratory infections, while subject to inaccuracies, is by no means useless. Some of the categories of illness used in this study were changed very little

by the laboratory data. Thus, afebrile coryza and afebrile pharyngitis were rarely associated with specific agents and potentially pathogenic bacteria were recovered relatively infrequently from these patients. The same was true for patients with a clinical diagnosis of nonstreptococcal exudative pharyngitis. These diagnoses, therefore, have inferential value with regard to laboratory tests and therapy. Similarly the clinical syndromes of acute febrile nonbacterial respiratory disease (A.R.D.), pharyngoconjunctivitis, and streptococcal pharyngitis were caused by specific agents, principally viral, in about one-half of the cases although the clinical distinction of specific agents was made for only 20% of viral and 60% of bacterial infections. Thus, the likelihood of clinically determining the group of patients with infections caused by identifiable agents is reasonably high.

Summary and Conclusions. One hundred and twenty-two acute respiratory illnesses among civilian adults in clerical, technical or professional positions in a large city were investigated by clinical and laboratory methods. Ten of them were caused by influenza viruses, 7 by beta-hemolytic streptococci, 4 by adenoviruses, 2 were serologically compatible with infectious mononucleosis and 6 were diagnosed clinically as Coxsackie virus infections. Of the entire group, 29 or approximately one-quarter of the patients had fever. Sixty-three, or 52%, were afebrile illnesses of unknown etiology in which acute coryza or sore throat was the predominant symptom. Twenty-seven illnesses or 22% were characterized by pharyngitis in which fever, pharyngeal exudate or conjunctivitis was present. Three diverse miscellaneous illnesses were recognized. Thus, 75% of the infections were caused by unknown or undetected agents; 19% by known viruses or diagnosable infections presumed to be viral and 6% by beta-hemolytic streptococci.

Among civilians the nonepidemic occurrence of febrile acute respiratory disease (ARD), pharyngoconjunctivitis and nonbacterial exudative pharyngitis was infrequently caused by adenoviruses. These data suggest that immunization with adenovirus vaccine would not substantially reduce acute respiratory diseases in a civilian population. Influenza viruses, types A, B, or C, caused one-fourth of the febrile illnesses.

Bacterial species other than hemolytic streptococci that are considered potentially pathogenic for human beings were isolated from 17% of subjects at the first clinic visit, and from 19% of another group one week later. They were most common among patients with febrile acute respiratory disease and conjunctivitis, but their etiological importance was considered doubtful.

The differentiation of common respiratory infections into distinct clinical syndromes has valuable diagnostic and therapeutic implications. The clinical identification of streptococcal pharyngitis was made in 60% while that of specific viral agents was 20%. The latter was little better than chance. However, persons suffering from one or another of the detectable viral infections were distinguished as a group quite clearly from persons with acute afebrile coryza or undifferentiated upper respiratory infection of unknown etiology.

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SUMMARIO IN INTERLINGUA

Le Etiologia De Commun Infectiones Respiratori In Un Population Adulte Civil

Methodos clinic e laboratorial esseva utilisate in le investigation de 122 casos de acute morbo respiratori inter le adultos civil in positiones cleric, technic, o professional in un grande citate. Dece del casos esseva causate per viruses de influenza, 7 per streptococcos hemolytic beta, 4 per adenoviruses, 2 esseva serologicamente compatibile con mononucleosis infectiose, e 6 esseva diagnosticate clinicamente como infectiones per virus Coxsackie. Ex le gruppo total, 29 patientes, *i.e.* approximativemente un quarto, habeva febre. In 63 casos, *i.e* in 52% del total, le morbo esseva afebril e de etiologia non cognoscite e coryza acute o mal de gurgite esseva le symptoma predominante. In 27 casos, *i.e.* 22% del total, le morbo esseva characterisate per pharyngitis con le presentia de febre, exsudato pharyngee, o conjunctivitis. Tres differente morbos miscellanee esseva recognoscite. Assi, 75% del infectiones esseva causate per non-cognoscite o non-detegite agentes, 19% per cognoscite viruses (incluse casos de diagnosticabile infectiones que esseva supponitemente virusal), e 6% per streptococcos hemolytic beta.

In le subjectos civil del studio, le occurrentia nonepidemic de febril acute morbo respiratori, de pharyngoconjunctivitis, e de exsudative pharyngitis nonbacterial esseva causate infrequentemente per adenoviruses. Le datos suggere que immunisation con vaccino de adenovirus non resultarea in un marcate reduction de acute morbo respiratori in un population civil. Viruses de influenza, del typos A, B, o C, causava un quarto del morbos febril.

Species bacterial (a parte streptococcos hemolytic) que es considerate como potentialmente pathogenic pro humanos esseva isolate ab 17% del subjectos al tempore de lor prime visita al clinica e ab 19% de un altere gruppo un septimana plus tarde. Illos esseva le plus commun inter patientes con febril morbo respiratori acute e conjunctivitis, sed lor signification etiologic esseva considerate como dubitose.

Le differentiation de commun infectiones respiratori in distincte syndromes clinic es de valor ab le puncto de vista diagnostic e etiam therapeutic. Le identification clinic de pharyngitis streptococcal esseva facite in 60% del casos, sed le identification de un specific agente virusal esseva obtenite in solmente 20% (e isto plus o minus per accidente). Tamen, individuos qui suffreva del un o del altere del detegibile infectiones virusal constitueva un gruppo clarmente distinguibile ab individuos qui suffreva de acute coryza afebril o de non-differentiate infection supero-respiratori de etiologia incognoscite.

SUMMARIO IN INTERLINGUA

(See page 261 for original article)

Amebiasis Como On Lo Vide In Le Sala De Consulta

Nos reporta nostre experientias con 60 patientes, vidite in nostre sala de consulta, qui habeva amebiasis in le phase subacute o chronic. Omnes, con 3 exceptiones, esseva symptomatic. Iste forma del morbo representa un importante problema clinic a causa de su incidentia e a causa de su potentialmente sever manifestationes. Nos sublinea le levitate del symptomas e le paucitate del constatationes objective, incluse illos observate per sigmoidoscopia e clysteres a barium (in le casos studiate per iste medios) e le absentia relative de alterationes hematologic. Le identification del morbo in le practica del sala de consulta ha essite surprendentemente frequente. Es signalate le frequentia de infectiones familial. Un alte indice de suspicion, un methodo satisfactori in le examine del feces, e un examinator experte es requirite pro establir e confirmar le diagnose in multes del casos.

AMEBIASIS AS SEEN IN AN OFFICE PRACTICE*

By R. Bretney Miller, M.D.
ASSOCIATE IN MEDICINE, GEORGE WASHINGTON UNIVERSITY MEDICAL SCHOOL
SENIOR ATTENDING PHYSICIAN, EMERGENCY HOSPITAL

(From the Department of Medicine, The George Washington University School of Medicine, Washington, D.C.)

In 1947, Mackie[8] gave a most timely report before this Association entitled "Tropical Disease Problems Among Veterans of World War II." The following year, Elsom[3] presented a comprehensive review of "Amebiasis As a Postwar Problem." They, and many others, voiced concern over the possibility of returning veterans being a host reservoir for the wide dissemination of amebiasis as well as other tropical infections. Now, a decade later, it can be said that these earlier forebodings have not materialized (Markell, Mullinger and Schneider[10]). However, the war and many other reports since these two excellent presentations have caused diagnostic thinking to be focused on tropical diseases as a potential everyday problem.

In summing up the first half century of our knowledge of amebiasis Faust[5] (1944) said that "the idea that amebiasis was strictly or primarily a tropical disease and usually manifested itself as a fulminating dysentery or a liver abscess became gradually modified. Little by little, as epidemiologic studies were carried out, the discovery was made that amebiasis is practically cosmopolitan in its distribution, although as a rule its incidence is higher and its clinical expressions are more severe in the tropics than in cooler climates. Dysentery and liver abscess were found to be only two of its more dramatic manifestations. There might be a history of an acute or subacute appendicitis or of general colonic distress without dysentery or even without diarrhea. There might be no apparent intestinal disturbance but a mild toxic state, with moderate leukocytosis and a low-grade fever. The patient might be considered symptomless by the uncritical diagnostician and yet at necropsy extensive amebic ulceration of the colon might be demonstrated. Throughout this period by direct and indirect methods there developed increasing evidence that *Endamoeba histolytica* is always actually or potentially a pathogen and that it is capable of invading and destroying the host's tissue without the aid of pathogenic bacteria."

It is the latter form of the disease that is the subject of this presentation. The patients are mine and those of my associates: Doctors Theodore Abernethy, Walter K. Myers, Thomas Hartman, and George Buchanan. These colleagues have contributed their case material to the study and I am indebted to them for their assistance and advice. In reviewing the literature, I found no similar report covering adult ambulatory private patients.

In the past, we have had the unrewarding, but by no means unique, experience of failing to obtain confirmation by positive stool findings in many patients with a suspected diagnosis. A

*Presented at the meeting of the American Clinical and Climatological Association on October 28, 1957, Hot Springs, Virginia.

number of these, perforce, had been treated on suspicion alone. A year and a half ago we were fortunate in acquiring the services of an expert parasitologist at Walter Reed Army Hospital who spends several evenings a week in the laboratory. This was the starting point and the one which gave impetus to this project.

No attempt was made to estimate the incidence rate in the practices of the five of us. Nor are any infection rates in the general population available for this area. However, during this period the parasitologist examined stools from 426 patients including those submitted by other physicians. Of the total, 148 (34.7%) were reported positive for *E. histolytica*.

A high index of suspicion of amebiasis requires frequent stool examinations. The indications for these are (1) a history of exposure in endemic areas, with or without dysentery, (2) systemic symptoms of headache, unexplained fever and easy fatigability, (3) gastrointestinal symptoms of nausea, abdominal cramps, increased flatus, irregular stools, and pruritus, and (4) a family history of close contact with another infected individual.

In a 16-month study period, from March 1, 1956, to July 1, 1957, 60 adult persons were found to have stool examinations positive for *Endamoeba histolytica*. Forty of these were women and 20, men. They were considered a representative sample of the middle and upper economic population group of the Washington area. The age span was from 17 to 87 years, with an average of 47.7.

A history of dysentery was notably absent in 36 (60%) and present in some degree in only 24 (40%); mild in 13, moderate in 2, marked in 3, and severe in 6. The sources of probable infection are shown in Table 1 with 30% occurring after travel abroad and 23% from unknown sources within the United States. All patients, except 2, were native-born United States citizens. It will be noted that this group is not unduly weighted because of the considerable number of foreign service officers seen in Washington. Only 13% were in that category. There was a history of exposure in 20% occurring within one year; in 18%, 2 to 5 years ago; in 15%, 5 to 10 years ago; in 16.7% more than 10 years and 2 of the patients dated their infections from the World's Fair in Chicago in 1933.

TABLE 1.—SOURCES OF PROBABLE INFECTION

Unknown, within USA	14 (23.3%)
Private travel abroad	18 (30.0%)
Foreign service of USA	8 (13.3%)
Folluted well (family)	6 (10.0%)
World War II veterans	3 (5.0%)
Family contacts	5 (8.3%)
Chicago World's Fair	2 (3.3%)
Food handler	1 (1.7%)
Laboratory infection	1 (1.7%)
Foreign diplomat in USA	1 (1.7%)
Foreign-born US citizen	1 (1.7%)

Symptoms were noted and in these frequencies: cramps in 58%, fatigue in 42%, some degree of diarrhea in 36%, with only 10 patients having more than 5 to 6 stools a day. Abnormal gas and flatus were present in 25% of the patients, nausea in 15%, and mucus, gross blood and pruritus each occurred in 8%.

Objectively, the physical findings were normal except for abdominal tenderness present in 36%, increased peristalsis in 8% and liver tenderness in 2%.

The symptoms and signs are nonspecific, often vague and unimpressive. It has been said that these patients are not sick and not well, with a clinical picture simulating functional gastrointestinal disturbances.

Sigmoidoscopy was performed in 11 patients. Ulceration, typical of amebic colitis, was seen only once. Barium enema studies were normal in 28 with loss of haustral markings consistent with amebic involvement found in only one. Blood counts were available on 53 of the 60 patients. The hemoglobin values were 13 gm. or above in 26 patients and no patient had less than 11 gm. Hematocrits were 40 or above in 36 patients, with none below the level of 36. Leukocyte counts were normal in 49, and between 10,000 and 12,500 in but 4 patients. Eosinophil counts were found in the range of 3% to 6% in 12 patients.

Fresh stool material was collected at home by the patient with directions to bring the specimen to the laboratory at his convenience, or immediately if the specimen were for culture. Instructions were to put a fecal bolus of approximately ½-inch or a liquid stool of ½-ounce in each of 3 small jars. The first jar contained polyvinal alcohol; the second, 10% formalin solution; and the third was reserved for culture or occult blood examination. Directions were given to emulsify the stool with a tongue blade in each of the two solution bottles. The methods employed for examination were Felsenfeld and Young's[6] modification of Mallory's hematoxylin-stained smear done on the polyvinal alcohol preparation, which fixes the trophozoites[6]. Secondly, the formalin-ether sedimentation method of Ritchie[12] was employed, which permitted examination of cysts on unstained slides or after staining with D'Antoni's Iodine[2].

These procedures avoid the necessity of warm stool examinations with their attendant difficulties, and allows multiple specimens to be examined at the convenience of the examiner. Permanently stained slides are made which may be re-examined indefinitely. In our experience these techniques have been superior to any of those previously employed in this laboratory.

The occurrence of positive stools in 3 examinations is shown in Table 2. In only 4 instances did 3 negative stools occur in succession, with the fourth one being positive. Small-race histolytica were found in 32 individuals, small and large race in one and large race in 27 individuals. While we did not have an exact tabulation, approximately 70% were estimated to be trophozoites, and 30% precystic and cystic forms (Young, Felsenfeld, Shales, Yoshimura and Stiehman[14]).

TABLE 2.—OCCURRENCE OF POSITIVE STOOLS

1st positive	44 (73 %)
1st neg. 2nd pos.	10 (17 %)
1st & 2nd neg. 3rd pos.	2 (3.3%)
1st, 2nd & 3rd neg. 4 pos.	4 (6.7%)
	60 (100 %)
Small race *E. histolytica*	32
Small & large race	1
Large race	27

Many workers in this field have emphasized the importance of the family in the epidemiology of amebiasis (Eyles, Jones and Smith[4], Mackie *et al.*[9], and Seckinger[13]). Craig[1] has stated, categorically, that "The finding of a single member of a family to be infected should be followed by the careful examination for this parasite in all the remaining members." To the well known dictum of the 4 F's: feces, fingers, foods, flies, by which amebiasis is transmitted, should be added a fifth; namely, *family contacts.*

In our series, 22 or more than 1/3 of the patients were members of infected families. Of these, there were 7 husbands and wives who had traveled in the same endemic areas

and in whom it seemed very likely that infection had occurred from a common source. There were several families which were of special interest and in which we believed that one member in all probability had infected the others.

There were 4 members in the "*E*" *family*, none of whom had been outside the United States. The wife was first seen in 1949 with severe acute dysentery. She was hospitalized and 5 examinations were negative for parasites, although the amebic complement fixation test was positive. She was treated with emetine, carbarsone, and Diodoquin with complete remission. Subsequent attacks occurred in 1953, 1955, and 1956, with the first positive stool for amebae being found during the last attack. Her husband was seen in March, 1956. He reported having had occasional mild diarrhea for 2 years. His stools were positive for cysts. The son and daughter had had mild bowel irregularities for several years. Trophozoites were found in each of their stools. It appeared from the data, though final proof is lacking, that the mother acquired the infection first, the others secondarily from her, and they, in turn, reinfected her. All members of the family were then treated simultaneously. Follow-up studies for one year indicated that they are now symptom-free and their stools have remained negative.

Another example of this problem was the "*W*" *Couple*. The wife was first seen in June, 1957, after having had "irritable bowel symptoms" for 1½ years. She had not been out of the United States. The husband, a World War II veteran of Italy and the South Pacific, gave no history of dysentery, but had had one or two stools a day with cramps, gas, and pruritus. The wife's stools contained large-race histolytica; and the husband's, both the large and the small strain. They are both symptom-free following two courses of Milibis and Aralen. We feel that follow-up period has not been adequate to justify a report on the result of posttreatment stool examinations.

In the "*A's*", a physician's family, the wife had diarrhea following a nephropexy and her stools were positive for *E. histolytica*. An older daughter, the only traveler, had had mild diarrhea 2 years before, after a visit to Southern France. Her stools were positive. The younger daughter's stools were positive; the father's were negative. Here it seemed very probable that 3 of the 4 had been infected by one member. Follow-up to date has been too short to appraise treatment results.

The "*McM*" *family* represented an unusual situation. They lived in a rural Maryland community with their own septic tank for sewage disposal. This was emptied at intervals and the contents used as garden fertilizer after the custom of the Orient. Six are included in this study though there were 13 people involved in this outbreak. All have been treated and the follow-up for 6 months has shown the stools of all but one individual to be negative.

TABLE 3.—COMMON ASSOCIATED CONDITIONS

Spastic colon	7
Allergic rhinitis	6
Urticaria	4
Duodenal ulcer, inactive	3
Arthralgia	2
Rheumatoid arthritis	2

Table 3 shows the common associated conditions. Of special interest is the relation of rheumatoid arthritis and amebiasis as pointed out by others (Rappaport, Rossien and Rosenblum[11]).

The case of an 87-year-old man who began for the first time with typical

manifestations of rheumatoid arthritis in the summer of 1953 illustrates the association. His sedimentation rate was 32 and had previously been under 20. He had no bowel symptoms but loose stools developed one year later. In Peru, in 1948, he had had mild dysentery, although upon his return to the United States no parasites were found in his stools. A traveling companion had had dysentery with positive stools. The arthritis followed a variable course with remissions and exacerbations, in one of which diarrhea occurred in the spring of 1957. Stools were then re-examined and *E. histolytica* found. He was given Aralen and Milibis with a flare reaction in the knee joints during the first 48 hours. He reported late in July that the arthritis symptoms had disappeared and an objective examination then and again in early October, 1957, showed the joints to be normal. Two posttreatment stool examinations have been negative.

Because of a relatively short follow-up period, in the majority of patients, little can be said about the long-term effects of the treatment. Our experience confirms that of others in that no wholly satisfactory agent is yet available. Chloroquin, the tetracyclines, carbarsone, Milibis, Diodoquin, and Fumagillin have been used in varying combinations. There have been a significant number of relapses. Perhaps this question of treatment results might well be the subject for a later report.

Summary. We have reported our experience with 60 office patients who had amebiasis in the subacute or chronic phase. All patients except 3 were symptomatic. This form of the disease is an important clinical problem because of its incidence and potentially severe manifestations. We stress the mildness of the symptoms and the paucity of objective findings, including those observed by sigmoidoscopy and barium enema in the patients so examined and the relative absence of hematologic changes. The disease has been found surprisingly often in an office practice. The frequency of family infections is emphasized. A high index of suspicion, a satisfactory method of stool examination, and a competent examiner will establish and confirm many a diagnosis.

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(Interlingua on page 261)

RELATIVE SIGNIFICANCE OF HEREDITY, DIET AND OCCUPATIONAL STRESS IN CORONARY HEART DISEASE OF YOUNG ADULTS

BASED ON AN ANALYSIS OF 100 PATIENTS BETWEEN THE AGES OF 25 AND 40 YEARS AND A SIMILAR GROUP OF 100 NORMAL CONTROL SUBJECTS

By Henry I. Russek, M.D.
CONSULTANT IN CARDIOVASCULAR RESEARCH, USPHS HOSPITAL, STATEN ISLAND, NEW YORK

AND

Burton L. Zohman, M.D.
ASSOCIATE CLINICAL PROFESSOR OF MEDICINE, STATE UNIVERSITY OF NEW YORK, COLLEGE OF MEDICINE AT BROOKLYN, BROOKLYN, NEW YORK

Not long ago atheromatosis was universally accepted as an irreversible and immutable process of aging. Thus, when coronary atherosclerosis was found in a young adult it was assumed that he had hurried through his life cycle developing the characteristics of old age at an accelerated rate. In such instances, hereditary influences, the stress and strain of modern life, over-eating and intemperance were usually considered adequate to account for premature "aging" of the coronary arteries. In recent years, however, the fatalistic assumption that atherosclerosis is an inevitable and inexorably progressive process of senescence has been abandoned in favor of the more hopeful view that its development is dependent on physical and chemical factors which may be reversed. It is now widely held that arteriosclerosis relates its origin to a disturbance in lipoid metabolism and more specifically in the metabolism of cholesterol. The epidemiologic studies of Keys and co-workers[8-15] have brought into focus the penalties of a luxurious high-fat diet. Nevertheless, it is becoming increasingly clear that other factors in the mode of living or environment, singly or in combination, may also contribute to the development of this disease in susceptible individuals. Recent attention has been drawn to the possible predisposing influence of sedentary living, habitual lack of physical exercise and poor health habits (Luongo[16]). Contrariwise, there has been increasing denial of the traditional view that hard work, over-exercise and emotional stress are causally related to the development of coronary artery disease (Arnott[2] and Keys[7]). Indeed, the whole concept that stress and strain may influence the time of onset or progression of atheromatosis has been challenged on the grounds that there is a complete absence of evidence for its validity. Arnott[2] has attributed the persistence of this concept to the psychological fact that it is far more consoling to the patient stricken with a coronary thrombosis to be told that "it is all due to hard work, laudable ambition, and selfless devotion to duty than to be told it is due to gluttony and physical indolence." Luongo[16], however, has expressed the view that stress must remain suspect in the etiological picture of coronary disease since nervous tensions at either an occupational, social or domestic level frequently lead to over-eating and overweight and affect the individual's outlook on healthful pursuits in life.

Moreover, his finding of obvious detectable stress patterns in most of the patients with coronary disease prior to their attack lends support to earlier recorded observations that many patients with acute coronary occlusion disclose a history of recent or prolonged psychic conflict and emotional tension (Arlow[1]). The validity of these findings, however, has not met with general acceptance because of the acknowledged difficulties in the assessment of psychological factors in the patient who has already suffered a coronary attack.

Leading authorities at present contend that stress and strain have always been an integral part of man's existence in all geographical areas and in every generation, reminding that "living in terror of being scalped was stressful as was building the pyramids." The omnipresence of "stress and strain" among all populations of the world has, therefore, been advanced as evidence that this factor plays little part in determining the epidemiological characteristics of coronary artery disease. Nevertheless, Gertler and White[5] in a careful analysis of possible causative factors leading to acute coronary occlusion in young adults have confirmed previous impressions that the disease is more likely to occur in individuals engaged in managerial and executive positions. From their observations "it cannot be stated with certainty whether the risks, mental strain and preoccupation of individuals in managerial positions are responsible for coronary heart disease or whether the ambitious, driving nature which culminates in a managerial post is actually an additional causative factor." White[18], however, while assigning major etiologic significance to deranged lipid metabolism, has recently expressed doubt that stress and strain play a significant role in the genesis of coronary heart disease. In sharp contrast, Russian observers[17] currently ascribe more importance to neurologic factors in the production of atherosclerosis than to dietary chemistry. While admitting that cholesterol is the prime culprit in lipoid infiltration of the arterial intima, they believe that lipoid-cholesterol metabolism is essentially disturbed by nervous or endocrine dysfunctions. Consequently, while there is little scientific basis for the clinician's impression and layman's conviction that mental stress or emotional disturbances predispose one to coronary artery disease, we do not yet possess sufficient evidence, either positive or negative, to rule out mental stress as an important factor in the occurrence or progression of this disorder. The possible relationship of physical and emotional stress to the development of coronary heart disease, therefore, is worthy of serious study because of its implications in prophylaxis and therapy. It is obvious that before preventive measures can be rationally instituted, recognition of the individual most prone to coronary heart disease will be necessary.

In order to gain insight into the possible etiologic and predisposing influences concerned with the development of clinical coronary disease, we like others, have searched for clues among patients afflicted at a relatively early age in life. During the past 10 years we have been afforded the opportunity of carefully studying the hereditary background, health habits and mode of life in 100 young adults with manifest coronary disease. The findings in this group have been compared with the data obtained in a contratest group of 100 persons with the same distribution of ages but without coronary disease.

Material. Of the 100 coronary patients, all but 3 were men. Their ages ranged from

25 to 40 years but approximately two-thirds of the group were over the age of 35. Classical myocardial infarction confirmed by electrocardiographic studies had occurred in 89 of the patients while 11 suffered from typical angina of effort without infarction. All of the cases represented instances of "pure" coronary heart disease since those with hypertension, diabetes, syphilis or valvular defects were excluded. All of the patients were seen by the authors in private practice, in consultation or on medical services of various hospitals. Eighteen of the 100 patients were referred by other physicians who shared our interest in this young coronary group. Evaluations and interviews were conducted during the late convalescent period following acute myocardial infarction or in succeeding months following the attack. The patients with angina pectoris without myocardial infarction were studied in similar manner while under treatment for their disorder. By this means answers were obtained to questions concerning health history, habits, diet, hereditary influences, sources of tension and events preceding the onset of clinical symptoms. For comparison, replies were obtained to identical questions in an unmatched control group of 100 healthy subjects of similar age, occupation and ethnic origin.

Results. HEREDITY. A definite history of cardiovascular disease in one or both parents was elicited in 67% of the 100 patients with coronary disease. In only 16% were both parents living and in normal health while in 17% death in one or both parents had occurred from noncardiac or unknown causes. In contrast, 40% of the control subjects gave a similar history of cardiovascular disease in one or both parents while 40% indicated that both parents were living and in normal health. In 20% of this group death in one or both parents had resulted from noncardiac or unknown causes. These findings are, therefore, in accord with the results of other studies which have demonstrated the strong influence of heredity in coronary heart disease. Contrariwise, it is also to be noted that good health and longevity in both parents did not invariably confer "immunity" even relatively early in life among the progeny. Thus, approximately 1 out of every 6 in this young coronary group gave such a favorable family history.

OBESITY AND BODY BUILD. At the time of onset of clinical symptoms, 26% of the patients were unmistakably obese as compared with 20% of the subjects comprising the control group. Manifest obesity *per se*, therefore, did not appear to be an important predisposing factor in the early development of coronary artery disease. Although detailed somatotype classification was not undertaken, the study revealed a decidedly higher incidence of muscular subjects with a tendency to obesity (endomorphic mesomorphs) in the patients with coronary disease than in the contratest group. This finding, therefore, lends confirmation to the observations of Gertler and White[5] regarding the higher frequency of this physique among young coronary patients.

DIET. Of the 100 young coronary patients, 53 had been accustomed to ingesting inordinate amounts of fat in the daily diet as judged from analysis of their food consumption prior to the onset of their attacks. In contrast, similar dietary extravagance was noted in only 20 of the 100 control subjects. It is apparent, therefore, that a prodigiously high-fat diet was followed by more than half of the subjects in our study who suffered from clinical manifestations of coronary disease before their forty-first birthday and that such dietary patterns were more than twice as prevalent in this group as they were in the contratest series. In the light of accumulating evidence this difference may well have etiologic significance.

OCCUPATION. Different occupations with different physical, emotional and mental demands have been suspected as pathogenetic factors in producing coronary disease. The measurement of stress due to fears, phobias, frustration,

anxiety and fatigue is most difficult to accomplish particularly in retrospect in the coronary patient. Nevertheless, it was clearly evident in this study that 91% of the test subjects had been under unusual occupational stress for varying periods prior to the onset of clinical symptoms. Thus, 25% of the patients not only had worked at full time jobs during the day but also had engaged in similar or different occupations during evening hours. An additional 46% of the coronary group had worked 60 hours or more per week for long periods immediately preceding clinical manifestations. In another 20% of the group there was unusual fear, insecurity, discontent, frustration, restlessness or inadequacy in relation to employment. In marked contrast only 20% of all the subjects in the control series showed comparable stress and strain in relation to occupation. This striking difference in the frequency of severe occupational strain, 4½ times more common in the coronary patients than in the controls, provided the main feature by which the two groups could be differentiated. Thus, the young coronary patient could not have been identified as readily by such factors as heredity (1.7 to 1), dietary fat (2.7 to 1), obesity (1.3 to 1), excessive smoking (2 to 1) or exercise (1 to 1) (Table 1). The following typical case histories illustrate the patterns of unusual occupational strain almost routinely observed among the patients in our coronary group:

TABLE 1.—INCIDENCE OF VARIOUS FACTORS IN CORONARY AND CONTROL GROUPS

	No.	*Heredity (positive)*	*High-Fat Diet*	*Stress & Strain (Occupational)*	*Obesity*	*Tobacco (30 cigs +)*	*Exercise*
Coronary Group	100	67%	53%	91%	26%	70%	58%
Control Group	100	40%	20%	20%	20%	35%	60%
Ratio		1.7 to 1	2.7 to 1	4.6 to 1	1.3 to 1	2 to 1	1 to 1

Case Reports. CASE 1. A 28-year-old Post Office employee was given his first assignment as a "substitute" on a parcel-post route. For a period of 6 months he worked 17 to 20 consecutive days before he would have one day off. He consumed a high fat diet but was not obese. Both parents were in normal health. He gradually manifested symptoms of coronary insufficiency which were misdiagnosed as "back-sprain" (because of the location of discomfort as well as his youth) until classical myocardial infarction developed.

CASE 2. A 30-year-old truck-driver continued in his usual trade while attempting to manage a small "night club" which he had purchased in partnership with a friend. His participation in the new venture necessitated irregular habits with only one or two hours of sleep on alternate nights. He was not obese and subsisted on a typical American diet. Family history disclosed no evidence of coronary heart disease. After 3 months, during which there were mounting financial pressures and dissension with superiors in regard to his day-time occupation, he suffered acute myocardial infarction.

CASE 3. A 39-year-old business executive engaged in market research had built up a highly successful business with his partner, after only a few years, as a result of working 70 hours a week or more. For 4 weeks prior to his attack, he frequently had worked round the clock in an attempt to meet a "deadline" in an advertising campaign. The day after completion of the project he was quite active preparing for a graduation party for his daughter on the occasion of which he suffered an acute coronary occlusion. Family history did not reveal a predisposition to coronary disease. The patient was not obese but ate a large quantity of dairy products routinely.

CASE 4. A 39-year-old dentist with a successful practice opened a second office in a neighboring town one-half hour's traveling distance from the first. His appointment schedule required that patients be seen in

both offices each day. For 6 months prior to his attack he experienced mounting tension as the result of increasing demands upon his services. He was not obese and was accustomed to an "average" American diet. Both parents were living and in normal health.

CASE 5. A 40-year-old business manager and accountant for a large industrial concern also worked 6 nights a week performing private accountancy and tax work for smaller concerns. He was markedly obese and subsisted on an exceedingly high-fat diet. One parent had coronary disease. He died on the second day of his attack.

CASE 6. A 39-year-old plumber working for the State of New York supplemented his income by playing in an orchestra 3 to 4 nights a week at weddings and parties. After eating a heavy evening meal at home he would enjoy a second banquet at the hotels in which he worked as a musician. After one year in this dual occupational role he sustained acute myocardial infarction. One parent had died from this disease.

CASE 7. A 25-year-old laborer who had worked for his father in road construction enterprises was forced to take over the full responsibilities of an insolvent business when his father suffered a coronary attack. This necessitated management of personnel, planning of jobs and collection and expenditure of funds in a failing business. He sustained a coronary occlusion less than one year after he had assumed these responsibilities.

CASE 8. A 40-year-old physician, anesthesiologist, had been on call 24 hours a day because of a lack of assistants adequately qualified to share his duties. After several weeks of broken sleep and long hours of work he developed coronary insufficiency. Family history indicated a predisposition to this disorder.

CASE 9. A 40-year-old executive sales manager for a large shoe chain worked at least 70 hours per week in attempting to justify his recent appointment to the new position. He had been under tremendous pressure often working throughout the night without sleep for several weeks prior to his fatal attack.

These cases as well as numerous others in the series clearly demonstrate the unreliability of occupational titles from the standpoint of correlating epidemiological data with any conclusive effects of occupation. In any true evaluation of these effects, account must be taken of deviations from usual hours of work, other occupations, and activities pursued during periods away from the job.

EXERCISE. Prior to the onset of their attack, 58% of the coronary patients exhibited regular exercise patterns either at work or away from the job. In 32% arduous physical activities were performed daily in the course of employment while in 26% exercise was obtained mainly by regular participation in sports. The remaining 42% of the coronary patients followed sedentary pursuits and did not indulge in regular exercise. In the control group, 60% of the subjects showed regular exercise patterns, 40% primarily as the result of occupation and 20% chiefly by participation in athletic activities. In the remaining 40% no regular exercise was performed either at work or at leisure. From these observations there is no indication that regular exercise, or the lack of it, plays a significant role in the genesis of coronary heart disease in young adults.

TOBACCO. Prior to the attack, 90% of the coronary patients indulged regularly in the use of tobacco, while 10% were either nonsmokers or participated on rare occasions. Among controls, on the other hand, 62% were habituated while 38% smoked occasionally or not at all. Heavy smokers were also found to be far more frequent in the coronary group. Thus, 70% of their number had smoked at least 30 cigarets per day prior to their attack as compared with only 35% in the contratest group. These observations indicate, therefore, that smoking was not only more prevalent in the coronary group but also that the coronary patients who had smoked were more heavily addicted to the use of tobacco. Nevertheless, it is not clear from these findings whether nicotine is a predisposing factor in coronary heart disease or whether its more frequent and excessive use among young

candidates is merely a reflection of the heightened emotional tension so prevalent among them.

Comment. It has long been recognized that coronary disease is notably more common among the children of parents for whom there is such a history and especially if both parents were so afflicted at a relatively early age. It is not known whether this predisposition is based on familial hypercholesterolemia, an excessively mesomorphic build, genetic inadequacy of the coronary arterial tree, hormonal influences, familial gluttony, or combinations of these or other factors as yet undiscovered (White[20]). Although the findings of the present study confirm the familial tendency to this disorder, they also clearly indicate that a favorable heredity does not preclude the development of coronary disease early in life in the progeny. Thus in 17 of the 100 young coronary patients both parents were living and in normal health. Consequently, other significant predisposing factors, in addition to heredity, must play a major role in the development of this disease. Data from the present investigation appear to indicate that emotional strain and a high-fat diet occupy a foremost position in this regard. Indeed, inasmuch as 62 of the 67 patients with a positive family history either were "victims" of an excessively high-fat diet or of undue emotional stress or both, it appears likely that relatively few individuals need be doomed to early coronary disease simply as a result of hereditary influences alone. On the other hand, by their way of life, susceptible persons may virtually invite atherogenesis. Thus it was found that half of the patients in the coronary group manifesting a familial tendency to the disease had been accustomed to inordinate amounts of fat in the diet and excessively long hours of work in one or more jobs.

From this study it would appear that 3 major predisposing factors influence the onset and progression of coronary atheromatosis in young adults, namely, heredity, diet and emotional strain. It is noteworthy that while 24% of the control subjects manifested none of these influences, one or more were unequivocally present in every patient in the coronary group without exception. Similarly, all 3 factors were observed in only 8% of the controls as compared with 33% of the coronary cases. Even more striking was the finding that at least 2 of the major factors were evident in 95% of the coronary patients and in only 12% of the control subjects. Taken individually, the most impressive feature serving to differentiate the young candidate for coronary disease is found in relation to occupational stress. Unusual emotional strain arising from occupational endeavors was present in over 90% of the test cases as compared with only 20% of the contratest group. Since "stress" in this study was assessed from hours of work, secondary occupations and unusual psychic disturbance and not from nebulous criteria, easily influenced by bias when viewed in retrospect, the validity of the data appears established. The case histories briefly described attest to the occupational "quick-sands" by which almost all of these patients were engulfed for varying periods just preceding the coronary attack. Consequently, it would appear that undue emotional strain associated with job responsibility is far more significant in the etiologic picture of coronary disease than heredity or a prodigiously high-fat diet.

It seems incredible, therefore, that epidemiologic studies have focused so little considered objective attention on the possible influence of emotional stress. In such studies, the possible im-

portance of this factor has been frequently brought up only to be summarily dismissed. Many capable clinicians have similarly repudiated the idea that the rising incidence of coronary disease may be correlated with the increased strain of modern living. Nevertheless, it has frequently been reported that many patients with acute coronary occlusion disclose a history of recent or prolonged psychic conflict and emotional stress. Coronary heart disease, therefore, like hypertension, peptic ulcer and hyperthyroidism has been viewed by some as a psychosomatic disease occurring in specific susceptible personality types (Arlow[1]). The coronary patient has been characterized as an aggressive, ambitious individual with an intense physical and emotional drive, unable to delegate authority or responsibility with ease, possessing no hobbies and concentrating all his thoughts and energy in the narrow groove of his career (Kemple[6]). Certainly, the experience gained from the present study indicates that the young coronary patient is usually a high-strung individual who has lived beyond his normal capacity and tempo, minimizing his symptoms and neglecting prudent rules of health. To assume that the difference in susceptibility to coronary disease between the Bantu and American male can be explained solely in terms of fat ingested in the diet is to presume that the human organism is a static apparatus which can be modified only by the substances put into it, and to ignore the profound effects of emotion on bodily function. Such a concept disregards those things in man that make him an "aspiring" as well as "suffering" being, possessing ideals, goals, values and social urges. Moreover, the same studies which have gained recognition for the role of diet, have shown that if job responsibility were used as an index, as good a correlation could be found between it and the increased incidence of coronary artery disease as was found with the fat intake (Brock and Bronte-Stewart[3]). Similarly, both the study of Gertler and White[5] and that of Yater and coworkers[21] have clearly shown a considerable difference in the type of civil positions held by young coronary patients as compared with controls. The young coronary patient almost always had occupied a position demanding responsibility and frequently associated with emotional stress. The influence of occupational stress in negating the astounding immunity of the premenopausal female has also been widely recognized by clinicians. The occurrence of acute coronary occlusion in the absence of hypertension or diabetes prior to the menopause is usually observed in women who have assumed the role of "head of the family" and have taken on the socioeconomic responsibilities of the male. This was precisely the finding in all 3 of the women included in the present series. It appears evident, therefore, that occupational strain and neglect of healthful habits of living as the result of the cares and distractions of an increasingly complex life are clearly reflected in the epidemiological characteristics of this disease.

Confirmation of the importance of daily occupational stress in the causation of acute coronary occlusion has been established by recent studies (Cathey[4] and Rosenman and Friedman[18]). Evidence has been presented by Rosenman and Friedman[18] which indicates that stresses imposed by modern business competition are responsible for blood patterns predisposing to coronary attacks. Their observations have shown that mounting tensions at work are associated not only with elevated blood cholesterol levels but also with an increased tendency of the

blood to clot. Cathey[4] has similarly observed that serum cholesterol levels are related to the life situation and to the individual's reaction to those situations. In patients with a history of myocardial infarction, periods of high serum cholesterol were almost invariably related to episodes of emotional stress. Aside from these undesirable effects, emotional stress may favor atheromatosis by altering the functional characteristics of the mode of life. It is well known that persons suffering from unusual nervous strain of occupational, cultural, social or domestic origin frequently reflect the inner tensions which beset them by overeating and by smoking or drinking to excess. Immoderate ingestion of fat may thus be superimposed on neurogenic disturbance of cholesterol metabolism and blood coagulability. On the other hand, from available evidence the increased consumption of tobacco by young candidates for the disease must be viewed simply as a manifestation of their heightened emotional tension rather than as a predisposing factor in the initiation or progression of atheromatosis.

Recent attention has been drawn to the possible role of sedentary living, habitual lack of physical exercise and poor health habits in the causation of coronary heart disease. Since such unhygienic patterns are frequently a byproduct of occupational stress, any apparent correlation which may be found between their presence and a predisposition to coronary disease may be dependent not on these factors *per se* but on the emotional influences responsible for their development. Bold claims have also been made regarding the value of exercise in the prevention of coronary atheromatosis and in the stimulation of collateral circulation following convalescence from myocardial infarction. The present study has given no indication that regular exercise or the lack of it, plays a significant role in the etiologic picture of this disease. Although exercise during leisure hours frequently provides relief from nervous tension for those engaged in sedentary occupations, its routine prescription for all persons appears both illogical and undesirable. The manual laborer and those engaged in other arduous physical activities would seemingly do far better to seek relaxation through less fatiguing channels. The business executive and white collar worker continuously exposed to long hours of work cannot justifiably be encouraged to exercise when the time required for such activity encroaches upon that needed for rest. Obviously, exercise regularly obtained under such circumstances may have no beneficial influence either in health or disease. Similarly, while the patient with coronary insufficiency may benefit from activities performed within the range of tolerance, the recent acclaim of the value of exercise has introduced many abuses. These have resulted from a failure to recognize that in no aspect of therapy is individualization more essential or routine practice more to be deprecated.

Summary and Conclusions. It is widely accepted that coronary atheromatosis relates its origin to a disturbance in lipoid metabolism and more specifically in the metabolism of cholesterol. Although heredity and diet are currently regarded as the only factors of major etiologic significance, it is becoming increasingly clear that other characteristics of the mode of living or environment, singly or in combination, may also contribute to the development of this disease in susceptible individuals. However, in contrast to the traditional view that coronary disease may be brought on prematurely by hard work, over-exercise and

emotional strain attention has been recently directed to the possible predisposing influence of sedentary living, habitual lack of physical exercise and poor health habits. In order to assess the significance of some of these factors, comparison was made of the hereditary background, health practices, diet, mode of life and sources of tension in 100 patients, between the ages of 25 and 40, with established coronary disease and a similar but unmatched control group of 100 normal subjects. The observations and conclusions derived from the analysis may be summarized as follows:

A. The onset and progression of coronary atheromatosis in our relatively young patients appeared to be dependent on 3 major predisposing factors, namely, heredity, a high-fat diet and emotional strain of occupational origin. At least 2 of these factors were present in 95% of the coronary cases as compared with a similar finding in only 12% of controls.

1. HEREDITY. A definite history of cardiovascular disease in one or both parents was obtained in 67% of the coronary patients as compared with 40% of the control subjects.

a) Inasmuch as 93% of the patients manifesting a familial tendency to the disease also exhibited other significant etiologic factors, relatively few persons appear doomed to early coronary attacks simply as a result of hereditary influences alone.

b) The finding that both parents were living and in normal health in 17% of the 100 coronary patients appears to indicate that by their way of life, "immune" as well as susceptible persons may virtually invite atherogenesis.

c) Although heredity exerts a strong influence in coronary heart disease, a positive history is not tantamount to a death sentence nor a negative history to a guarantee of longevity.

2. DIETARY FAT. Of the 100 young coronary patients, 53% were accustomed to inordinate amounts of fat in the diet as compared with only 20% of those comprising the control group.

3. OCCUPATIONAL STRESS. Severe emotional strain of occupational origin was observed in 91% of the test subjects as compared with 20% of normal controls.

B. Emotional stress associated with job responsibility appears far more significant in the etiologic picture of coronary disease in young adults than heredity or a prodigiously high-fat diet. Almost without exception, the young coronary patient was found to be an aggressive, ambitious individual who had lived beyond his normal capacity and tempo.

C. Inability to quantitate emotional stress by laboratory methods does not justify its arbitrary dismissal as a possible predisposing factor in the development of coronary atheromatosis. The stresses imposed by modern business competition have been found responsible for neurogenic disturbance of cholesterol metabolism and blood coagulability.

D. Manifest obesity does not appear to be an important etiologic influence in the development of coronary disease in young adults.

E. Regular exercise, or the lack of it, showed no correlation with normal health or early coronary disease in the present study. The recent enthusiastic endorsement of exercise as a health measure has had harmful effects for cardiac patients whose management is not meticulously individualized. Exercise, even in normal health, may have little value if routinely obtained at the expense of needed physiologic rest.

F. Smoking of tobacco was not only more prevalent in the coronary group but also greater addiction among those who smoked. Excessive consumption of

tobacco, however, would appear to be an indication of heightened emotional tension rather than a predisposing or causative factor in coronary heart disease.

G. Re-orientation is needed in epidemiologic studies which ignore the profound effect of socioeconomic stress on bodily function and human behavior.

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SUMMARIO IN INTERLINGUA

Le Signification Relative De Hereditate, De Dieta, e De Stress Occupational In Morbo Coronari Del Corde In Juvene Adultos

Basate Super Le Analyse De 100 Patientes De Etates De Inter 25 e 40 Annos e De Un Simile Gruppo De 100 Normal Subjectos De Controlo

Es extensemente acceptate como un facto establite que le origine de atheromatosis es relationate a un disturbation del metabolismo lipoide e plus specificamente del metabolismo de cholesterol. Ben que al tempore presente le factores de hereditate e de dieta es reguardate como le sol factores de major signification etiologic, il deveni de plus in plus clar que altere characteristicas in le modo del vita o in le milieu, individualmente o in combination, pote etiam contribuer al

disveloppamento del morbo in individuos qui es susceptibile de contraher lo. Tamen, per contrasto con le notion traditional que morbo coronari pote esser generate prematurmente per travalios dur, excessos de exercitio, e stresses emotional, ha signalate plus recentemente le possibile influentia predispositori de un vita sedentari, del manco habitual de exercitio physic, e de insalubre habitudes hygienic. Pro clarificar le signification de certes de iste factores, un comparation esseva facite con respecto al fundo de hereditate, al practicas de hygiene, al modo de vita, e al causas de tension inter (1) 100 patientes de etates de inter 25 e 40 annos con establite morbo coronari e (2) un simile, ben que non appareate, gruppo de 100 normal subjectos de controlo. Le observationes e conclusiones derivate ab le analyse pote esser summarisate sequentemente:

A. Le declaration e le progresso de atheromatosis coronari in nostre relativemente juvene patientes pareva depender de 3 major factores predispositori, *i.e.* hereditate, dieta ric in grassia, e tension emotional de origine occupational. Al minus 2 de iste factores esseva presente in 95% del casos coronari, in comparation con un simile constatation in solmente 12% del subjectos de controlo.

1. HEREDITATE. Un definite historia de morbo cardiovascular in un o ambe parentes esseva obtenite in 67% del patientes coronari, comparate con 40% del subjectos de controlo.

a) Viste que 93% del patientes qui manifestava un tendentia familial a disveloppar iste morbo exhibiva simultaneemente altere significative factores etiologic, un relativemente basse numero de personas pare esser condemnate a suffrer precoce attaccos coronari simplemente como resultato de influentias hereditari sol.

b) Le constatation que ambe parentes viveva e se trovava in normal stato de sanitate in 17% del 100 casos de patientes coronari pare indicar que personas "immun" si ben como personas susceptibile pote virtualmente invitar le declaration de atherogenese per medio de lor modo de viver.

c) Ben que le hereditate exerce un forte influentia in morbo coronari del corde, un historia positive non es un condemnation a morte, e un historia negative non es un garantia de longevitate.

GRASSIA DIETARI. Ex le 100 juvene patientes coronari, 53% esseva accostumate a ingerer excessive quantitates de grassia in lor dieta, comparate con solmente 20% del individuos in le gruppo de controlo.

B. Stresses emotional del typo associate con responsabilitates occupational pare esser multo plus significative in le concatenation etiologic de morbo coronari in juvene adultos que le factores de hereditate e de dietas que es prodigiosemente ric in grassia. Quasi sin exception, le juvene patiente coronari se revelava como un individuo aggressive e ambitiose qui habeva vivite in ultra de su capacitate e de su tempo normal.

C. Le facto que stresses emotional non pote esser quantificate per methodos laboratorial non justifica lor rejection arbitrari como un possibile factor predispositori in le disveloppamento de atheromatosis coronari. Il ha essite constatate que le stresses imponite per le rivalitates del moderne vita commercial e industrial es responsabile pro disturbationes neurogenic del metabolismo de cholesterol e del coagulabilitate del sanguine.

D. Manifeste grados de obesitate non pare esser un importante influentia etiologic in le disveloppamento de morbo coronari in juvene adultos.

E. Regularitate de exercitio, o le absentia de illo, non exhibiva ulle correlation

con statos normal de sanitate o con le presentia precoce de morbo coronari. Le recente approbation enthusiastic de exercitio como un mesura de hygiene ha habite effectos nocive pro patientes cardiac in le casos de qui le regime de therapia non es meticulosemente individualisate. Exercitio, mesmo in le presentia de un normal stato de sanitate, non es necessarimente de valor si illo es obtenite al expensa del naturalmente requirite reposo physiologic.

F. Le uso de tabaco esseva non solmente plus prevalente in le gruppo coronari, sed etiam le grado de addiction esseva plus marcate inter le fumatores de ille gruppo. Tamen, excessos in le consumption de tabaco pare esser un indication de augmentate tensiones emotional plus tosto que un factor predispositori o causative in morbo coronari del corde.

G. Un desiderato urgente es le re-orientation de studios epidemiologic que neglige le profunde effectos del stresses socio-economic super le functiones corporee e le comportamento human.

SUMMARIO IN INTERLINGUA

(See page 290 for original article)

Relation Inter Le Unda P e Le Volumine Sinistro-Atrial in Rheumatic Morbo Cardiac Con Stenosis Mitral

1. Le relation inter le character del unda P e le volumine del atrio sinistre esseva studiate in 20 personas con rheumatic morbo cardiac, stenosis mitral, e normal rhythmo sinusal.

2. Incision del unda P esseva le anormalitate le plus commun e alte amplitude le minus commun.

3. Incision, amplitude, e duration del unda P non esseva correlationabile con le grado del allargamento sinistro-atrial.

4. Le axe electric de P esseva communmente semivertical, a vices vertical, rarmente horizontal.

5. Un complexo qR in le derivation V_1 non es relationate al grado del allargamento sinistro-atrial, sed illo es associate con marcate grados de hypertension pulmonar, allargamento dextero-atrial, e augmento del dimensiones cardiac.

6. Il existe le tendentia que le allargate atrio sinistre es associate con deviation dextrorse de P, sed le melior, ben que pauco marcate, correlation es illo con un deviation dextrorse de QRS in association con un quasi equal deviation dextrorse de P.

RELATIONSHIP OF THE BLOOD PRESSURE TO WEIGHT, HEIGHT AND BODY BUILD IN APPARENTLY HEALTHY SUBJECTS, 65–106 YEARS OF AGE

By Arthur M. Master, M.D.

and

Richard P. Lasser, M.D.

(From the Department of Medicine of the Mount Sinai Hospital, New York, New York)

The relationship of the blood pressure to the height, the weight and the body build of subjects who are more than 65 years old has hitherto not been described. Many studies of those who are under 65 have shown that: (a) there is a rise in the systolic and diastolic pressures as the weight increases in both men and women (Alvarez and Stanley[2], Boynton and Todd[7], Dunham[16], Hartman and Ghrist[19], Huber[20], Hunter and Rogers[22], Ley[27], Master, Dublin and Marks[29], Preble[41], Robinson, Brucer and Mass[44], Schnurman[45], Short and Johnson[47], and Symonds[48]); (b) there is a higher mortality associated with increased weight because of a greater incidence of degenerative and metabolic disease such as atherosclerosis, hypertensive cardiovascular disease and diabetes mellitus (Blair and Haines[6], Dublin and Marks[12,13,14], McCormick[36], Tr. Assn. Life Ins. Med. Dir. and Actuarial Soc. America[52,53]); and (c) there is a steady rise in the number of the obese, and an increase in the average weight of the general population with advancing age, certainly until age 50 (Hunter and Rogers[22] and Symonds[48]).

Because excess weight and obesity are now recognized as medical problems, it is important to study their general incidence. If by overweight is meant an increase of more than 10% above the average weight of adults of the same age, sex and height, about one-fifth of the population over the age of 30 is overweight. If by obesity is meant an increase of more than 20% above the average weight, more than 5 million adults in the United States are pathologically obese (Armstrong *et al.*[3]).

The pioneering work of the medical and actuarial departments of the insurance companies has clearly shown a direct relationship between obesity and a shortened life span[52].

Their studies are possibly more reliable than purely clinical observations in evaluating the ultimate effects of minor physical impairments, such as overweight, because they are essentially long-range studies, and are based upon a large number of subjects; the initial selection of the subjects and the subsequent evaluation of the findings are entirely independent and objective; the subjects are selected after medical examination, are presumably healthy, are in better than average circumstances, are free from serious defects, and are in safe occupations (Marks[28]). The insurance studies, however, mainly, if not only, cover subjects who are less than 65 years old, and hence, end at the point where this study begins.

The present study of persons over 65 years of age has many features that approximate those of the actuarial and medical departments. We, too, have a

considerable amount of data. The subjects who were selected by physicians, were apparently healthy persons living in the community, were ambulatory, and were clinically free of any cardiovascular-renal defects. Our results, like theirs, thus establish the relationship of the blood pressure to height, weight and body build within an apparently healthy though more aged group. Similar studies of persons over 65 years who do have various forms of cardiovascular disease are now in progress.

Master, Lasser and Jaffe[33] previously presented a statistical analysis of the blood pressure in this same group of subjects. It was found that women, at all ages over 65 years, had a higher systolic pressure, but essentially a similar diastolic pressure to that of men. The mean systolic blood pressure did not continue to rise with age after 70, and the mean diastolic pressure remained constant after the 65th year in both sexes. This was in sharp contrast to the findings in adults from 16 to 64, which were the subjects of a previous study[29] in which it was shown that both the systolic and the diastolic pressures rose steadily with advancing age in both sexes. These two studies thus served to establish the relationship of blood pressure to age and sex in adult life. Against this background, the relationship of the blood pressure to height, weight and body build will now be presented. The current report is one facet of a comprehensive study of the blood pressure in persons over 65 years of age.

Materials and Methods. Our data were gathered by means of questionnaires mailed to physicians throughout the United States. Each was asked to record the age, the blood pressure, the height and the weight of 3 persons over 65 years of age who lived in the community, were in apparently good health and were ambulatory at the time of the survey, and to furnish detailed medical information and other specific facts. The criteria used to select the healthy subjects from the total number of cards returned (15,000) were previously reported. In brief, those who were bedridden, those who had an acute disease or any clinical symptoms of cardiovascular disease and those who were in homes and hospitals for the aged were excluded. The number of apparently healthy subjects finally accepted for this study was 5,612; 2,922 males and 2,690 females. The statistical evidence of the internal homogeneity of the sampling and the authentication of the group selected as representative of the aged, noninstitutionalized, white population of the United States were also presented in an earlier paper.

The blood pressures were casual readings taken in the physician's office. We had requested that an atmosphere of calm be maintained, and that the subject be allowed a short rest before the examination. The systolic pressure was taken at the onset of the Korotkoff sounds and the diastolic pressure at the disappearance of sound (5th phase). We had also requested that only a new or a recently recorded pressure be furnished us, and that it be read to the nearest 2 mm. Hg. The patient's height was to be recorded in stockinged feet, the weight with the patient clad only in light undergarments. The weight of these undergarments was not subtracted. All subjects were divided according to sex and subdivided into 5-year age groups from 65 to 89 years. All subjects 90 years and over were grouped together because of the paucity of data at these ages. Subjects in each 5-year age group were then classified into one of 3 height groups: the males measuring up to 65 inches and the females up to 61 inches were classified as *short*; the males who were 66 to 70 inches tall and the females who were 62 to 66 inches tall were classified as of *average height*; the males who were 71 inches or taller and the females who were 67 inches or taller were classified as *tall*. These height groupings were used because they had been adopted generally by insurance companies. The mean or average weight was then obtained for all subjects in the same height group, regardless of age. The males of short height had a mean weight of 144 pounds; those of the average height group had a mean weight of 155 pounds; and those of the tall group had a mean of 171 pounds. The females of the short group had a mean weight of 127 pounds; those of the average height group had a mean weight of 137 pounds; the mean of those of the tall group was 152 pounds. From these mean

TABLE 1

HEIGHT AND WEIGHT GROUPINGS, 65-106 YEARS

Weight Group	Mean Weight pounds	Underweight pounds	Average Weight pounds	Mod. Overweight pounds	Severe Overweight pounds
MALES					
Short (65" and under)	144	<129	130-158	159-179	>180
Medium (66" - 70")	155	<139	140-170	171-193	>194
Tall (71" and over)	171	<153	154-188	189-213	>214
FEMALES					
Short (61" and under)	127	<114	115-139	140-158	>159
Medium (62" - 66")	137	<123	124-150	151-171	>172
Tall (67" and over)	152	<136	137-167	168-189	>190

Mean Weight represents the average of each respective height group of all subjects 65 years and over.
Underweight group: 10% or less lighter than the mean weight of the respective height group.
Average weight group: 9% lighter to 9% heavier than the mean weight of the respective height group.
Mod. Overweight group: 10% to 24% heavier than the mean weight of the respective height group.
Severe Overweight group: 25% or more heavier than the mean weight of the respective height group.

weights 4 weight groups were evolved in each height group: 1) an *underweight* group, which comprised subjects who were 10% lighter than the mean weight of their height group; 2) an *average weight*, which comprised subjects whose weight ranged from 9% less, to 9% above the mean weight of their respective height group; 3) a *moderate overweight* group, which included subjects who were from 10% to 24% above the mean weight of their height group; 4) a *severe overweight* group, which included all subjects who were more than 25% heavier than the mean of their height group. These values are shown in Table 1. In this classification the weight is related to the height, that is, an underweight person is considered to be underweight for his height. Since the mean weight increases with the mean height, a tall underweight person actually weighs more than a short person who is underweight. The significance of this will be demonstrated. The same method of analysis was used in an earlier study of subjects between the ages of 16 and 64 (Master, Dublin and Marks[29]).

The mean or average blood pressure and the standard deviation* were then calculated separately for each of the 12 subgroups, formed by the 3 height groups and the 4 weight groups in each 5-year age group, and for both sexes. The percentage of subjects in each of the height and weight groups was also computed for each 5-year age group. The statistical significance of all the observations was determined by establishing the reliability of the difference between sample means in the customary manner.

Results. A. RELATION OF SYSTOLIC AND DIASTOLIC PRESSURE TO WEIGHT. The mean blood pressures found in subjects in each primary weight, height and sex, 5-year age group are shown in Table 2. In each age group and in both sexes it can be seen that, as a general rule, the mean systolic and diastolic pressure increase with increasing weight. Deviations from this general rule are found only among those primary groups which are numerically very small and are believed to represent fluctuations due to small numbers. The magnitude of the increase of blood pressure with increasing weight is shown in Table 3 where subjects of all ages have been grouped into their respective height-weight groups. It is permissible to group all ages together in this fashion because it has been previously demonstrated that the average blood pressure level undergoes very little change with age after 65. Thus, any differences between the various height-weight groups in age composition will not influence their differences in blood pressure.

Underweight males have the lowest systolic and diastolic pressure in each height group, that is, underweight short males 141/78, medium height, 139/79 and tall males 139/79. The systolic and diastolic pressure of *average weight* males is somewhat higher than the underweights in each height group, that is, average weight short males, 146/80, medium height, 145/82 and tall males, 145/82.

Moderately overweight males show a further increase in average systolic pressure among short and medium height males while the tall moderately overweight is the same as the tall average weight group. Diastolic pressures of the moderately overweight in the three height groups are higher than those of average weight. The severely overweight males have the highest average systolic and diastolic pressure, that is, 151/85 among the short, 150/85 among the medium height and 153/87 among the tall severely overweight males. The average difference in the mean systolic and diastolic pressure between the underweight and the severely overweight male groups is about 10 mm. Hg (systolic) and 7 mm. Hg (diastolic).

In general, similar pressure changes occurred among females though both

*The standard deviation is a commonly used measure of the dispersion of values about the mean. One standard deviation above and below the mean includes about 67% of all values. The term $\pm \sigma$ will be used to indicate one standard deviation.

TABLE 2

MEAN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

ACCORDING TO HEIGHT AND WEIGHT, BY 5 YEAR AGE GROUPS

Height-Weight Classification	65-69		70-74		75-79		80-84		85-89		90+	
	No.	Mean mm,Hg	No.	Mean mm,Hg	No.	Mean mm,Hg	No.	Mean mm,Hg	No.	Mean mm,Hg	No.	Mean mm,Hg
MALES												
SYSTOLIC PRESSURE												
SHORT HEIGHT:												
Underweight	(46)	137	(40)	141	(25)	137	(26)	143	(33)	145	(25)	144
Average weight	(111)	144	(73)	152	(66)	145	(49)	148	(43)	147	(18)	139
Mod. overweight	(55)	150	(29)	159	(19)	149	(8)	138	(5)	146	(3)	164
Severe overweight	(21)	148	(17)	154	(12)	149	(-)	-	(2)	148	(2)	161
MEDIUM HEIGHT:												
Underweight	(88)	135	(88)	139	(87)	139	(69)	142	(46)	143	(38)	141
Average weight	(257)	144	(205)	144	(169)	148	(132)	146	(89)	146	(27)	146
Mod. overweight	(104)	146	(90)	149	(43)	148	(39)	148	(17)	150	(6)	161
Severe overweight	(26)	145	(30)	151	(19)	153	(3)	158	(7)	153	(2)	150
TALL HEIGHT:												
Underweight	(33)	137	(26)	134	(17)	139	(16)	138	(23)	142	(9)	156
Average weight	(89)	142	(55)	146	(45)	145	(25)	152	(37)	146	(13)	147
Mod. overweight	(48)	147	(25)	141	(18)	148	(7)	146	(11)	139	(-)	-
Severe overweight	(10)	156	(4)	146	(-)	-	(2)	150	(-)	-	(-)	-
TOTAL	(888)		(682)		(520)		(376)		(313)		(143)	
DIASTOLIC PRESSURE												
SHORT HEIGHT:												
Underweight	(46)	77	(40)	80	(25)	77	(26)	81	(33)	75	(25)	78
Average weight	(111)	81	(73)	83	(66)	78	(49)	82	(43)	78	(18)	75
Mod. overweight	(55)	83	(29)	88	(19)	81	(8)	79	(5)	82	(3)	95
Severe overweight	(21)	85	(17)	87	(12)	81	(-)	-	(2)	72	(2)	95
MEDIUM HEIGHT:												
Underweight	(88)	80	(88)	78	(87)	79	(69)	80	(46)	83	(38)	77
Average weight	(257)	83	(205)	82	(169)	82	(132)	83	(89)	79	(27)	82
Mod. overweight	(104)	84	(90)	84	(43)	83	(39)	82	(17)	81	(6)	78
Severe overweight	(26)	83	(30)	84	(19)	89	(3)	91	(7)	92	(2)	80
TALL HEIGHT:												
Underweight	(33)	81	(26)	79	(17)	80	(16)	75	(23)	81	(9)	77
Average weight	(89)	83	(55)	84	(45)	82	(25)	84	(37)	78	(13)	82
Mod. overweight	(48)	86	(25)	84	(18)	84	(7)	86	(11)	83	(-)	-
Severe overweight	(10)	88	(4)	84	(-)	-	(2)	90	(-)	-	(-)	-
TOTAL	(888)		(682)		(520)		(376)		(313)		(143)	
FEMALES												
SYSTOLIC PRESSURE												
SHORT HEIGHT:												
Underweight	(54)	149	(54)	157	(53)	157	(53)	159	(50)	156	(35)	149
Average weight	(100)	153	(86)	162	(63)	158	(47)	161	(29)	153	(15)	150
Mod. overweight	(83)	155	(43)	160	(22)	163	(18)	160	(12)	140	(-)	-
Severe overweight	(43)	155	(23)	155	(14)	166	(5)	161	(-)	-	(2)	140
MEDIUM HEIGHT:												
Underweight	(98)	150	(93)	151	(74)	149	(77)	152	(61)	151	(42)	152
Average weight	(240)	155	(207)	160	(127)	159	(83)	158	(55)	157	(26)	153
Mod. overweight	(96)	156	(75)	160	(49)	158	(23)	160	(19)	164	(9)	148
Severe overweight	(62)	160	(32)	163	(18)	169	(6)	164	(4)	146	(5)	148
TALL HEIGHT:												
Underweight	(12)	149	(18)	157	(12)	141	(7)	148	(9)	139	(-)	-
Average weight	(34)	156	(23)	163	(12)	152	(12)	152	(9)	165	(7)	155
Mod. overweight	(11)	161	(9)	161	(5)	173	(3)	153	(3)	134	(-)	-
Severe overweight	(8)	160	(5)	163	(4)	163	(2)	154	(-)	-	(-)	-
TOTAL	(841)		(668)		(453)		(336)		(251)		(141)	
DIASTOLIC PRESSURE												
SHORT HEIGHT:												
Underweight	(54)	80	(54)	82	(53)	83	(53)	84	(50)	82	(35)	80
Average weight	(100)	83	(86)	86	(63)	86	(47)	82	(29)	82	(15)	79
Mod. overweight	(83)	85	(43)	82	(22)	80	(18)	83	(12)	74	(-)	-
Severe overweight	(43)	87	(23)	82	(14)	88	(5)	90	(-)	-	(2)	85
MEDIUM HEIGHT:												
Underweight	(98)	82	(93)	84	(74)	81	(77)	81	(61)	79	(42)	81
Average weight	(240)	86	(207)	85	(127)	85	(83)	84	(55)	85	(26)	81
Mod. overweight	(96)	87	(75)	88	(49)	84	(23)	84	(19)	91	(9)	82
Severe overweight	(62)	88	(32)	89	(18)	91	(6)	85	(4)	82	(5)	81
TALL HEIGHT:												
Underweight	(12)	80	(18)	86	(12)	78	(7)	81	(9)	82	(-)	-
Average weight	(34)	88	(23)	86	(12)	83	(12)	87	(9)	87	(7)	78
Mod. overweight	(11)	87	(9)	95	(5)	88	(3)	90	(3)	73	(-)	-
Severe overweight	(8)	95	(5)	95	(4)	90	(-)	-	(-)	-	(-)	-
TOTAL	(841)		(668)		(453)		(336)		(251)		(141)	

TABLE 3

MEAN BLOOD PRESSURE ACCORDING TO HEIGHT AND WEIGHT FOR ALL AGES OVER 65 YEARS

TABLE 3

MEAN BLOOD PRESSURE ACCORDING TO HEIGHT AND WEIGHT FOR ALL AGES OVER 65 YEARS

Height-Weight Classification	MALES No.	MALES Systolic mm.Hg	MALES Diastolic mm.Hg	FEMALES No.	FEMALES Systolic mm.Hg	FEMALES Diastolic mm.Hg
SHORT HEIGHT:						
Underweight	(195)	141	78	(299)	155	82
Average weight	(360)	146	80	(340)	157	84
Mod. Overweight	(119)	151	84	(178)	157	83
Severe Overweight	(54)	151	85	(87)	157	86
MEDIUM HEIGHT:						
Underweight	(416)	139	79	(445)	151	82
Average weight	(879)	145	82	(738)	157	85
Mod. Overweight	(299)	148	83	(271)	158	87
Severe Overweight	(87)	150	85	(127)	161	88
TALL HEIGHT:						
Underweight	(124)	139	79	(58)	148	82
Average weight	(264)	145	82	(97)	157	86
Mod. Overweight	(109)	145	85	(31)	158	88
Severe Overweight	(16)	153	87	(19)	161	94

Underweight group: 10% or less lighter than the mean weight of the height group.
Average weight group: 9% lighter to 9% heavier than the mean weight of the height group.
Mod. Overweight group: 10% to 24% heavier than the mean weight of the height group.
Severe Overweight group: 25% or more heavier than the mean weight of the height group.

the systolic and the diastolic pressures were higher among females in each comparable height-weight group. The smallest differences in pressure among the 4 weight groups are found in the short female group, in which average, moderately overweight and severely overweight subjects all have the same systolic pressure (157 mm. Hg), while the mean systolic pressure of the underweight group is only 2 mm. Hg less. In the other height groups, however, a stepwise rise in systolic and diastolic pressure with increasing weight was found.

B. RELATION OF BLOOD PRESSURE TO HEIGHT. The mean systolic blood pressure of all subjects in each of the 3 height groups was computed and is shown in Fig. 1. The pressure in each height group was essentially the same. Diastolic pressure, too, did not vary with height. Height, therefore, bears little or no relationship to blood pressure.

C. RELATION OF BLOOD PRESSURE TO BODY BUILD. From Table 3 it is evident that for each sex, short underweight subjects, medium height underweight subjects and tall underweight subjects all have similar pressures, as do the average weight subjects and moderately and severely overweight subjects of each height group. As an example, the short average weight males have a mean pressure of 146/80, the medium height average weight males and the tall average weight males each have a mean pressure of 145/82 mm. Hg. This indicates that it probably is not the absolute weight which affects the blood pressure, since taller subjects weigh more than shorter ones in comparable "weight" groups, for example, the short average weight male group weighs from 130 to 158 pounds, averaging 144 pounds, and the tall average weight male group weighs from 154 to 188 pounds, averaging 171 pounds. Conversely, those having similar absolute

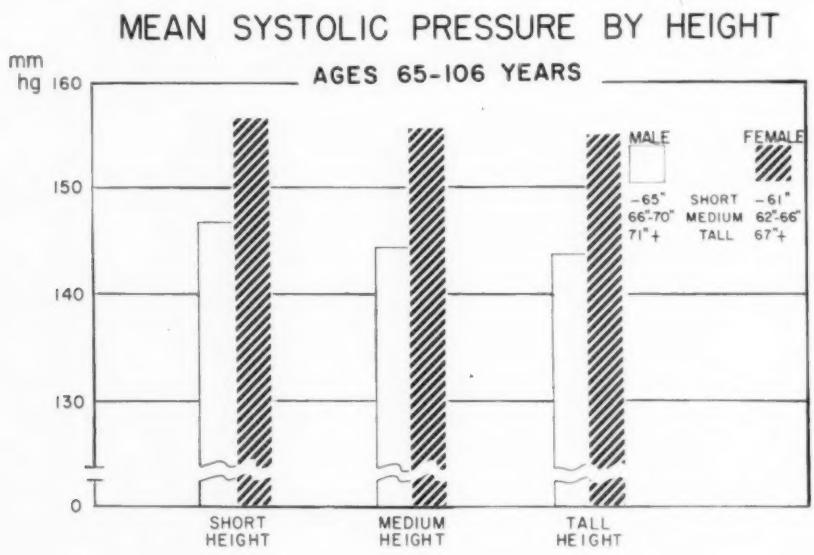

Fig. 1

weights, as the tall underweight and the short average weight subjects, do not have similar pressures. It is rather the *relative weight* (weight in relation to height) that is the true determinant which influences the blood pressure. We consider these height-weight groups as body build groups.

Discussion. Systolic and diastolic pressures have been found to increase with increase in weight (relative to height) in persons over 65 years of age. This is in complete accord with the observations made in younger adults (Alvarez and Stanley[2], Boynton and Todd[7], Dublin, Fisk and Kopf[11], Dunham[16], Faber[17], Hartman and Ghrist[19], Huber[20], Hunter[21], Hunter and Rogers[22], Ley[27], Master, Dublin and Marks[29], Master and Oppenheimer[34], Preble[41], Robinson, Brucer and Mass[44], Schnurman[45], Short and Johnson[47] and Symonds[48]). It applies not only to the white population, but also to the Chinese (Cadbury[9], and Kilborn[25]) and other races (Kean[23]). The difference found in the blood pressure between the underweight and the severely overweight aged (about 10 mm. Hg systolic and 7.8 mm. Hg diastolic) is also similar to that found in younger adults (Master, Dublin and Marks[29], Master, Garfield and Walters[30], and Symonds[48]).

The 4 weight subgroups, that is, underweight, average weight, moderate overweight and severely overweight, do not represent classifications based solely on absolute weight. The terms denote specific deviations in either direction from the mean weight of all persons 65 and over for a given height. Since these classifications encompass both height and weight, they constitute "body build" groups. Thus, blood pressure has been shown to vary directly with body build, and not with weight alone. We are aware that far more complex delineations of body build are possible than that based on height and weight only. Measurements of the girth of the thorax and of the abdomen, of the length of the torso and of the lean body mass (Brozek and Keys[8]) have been made, but as yet the data gathered are insufficient to evaluate the significance of these refinements. The data pertaining to the blood pressure of the height-weight groups used in this study are, on the contrary, extensive.

The question arises as to whether the magnitude of the blood pressure variation with body build, in apparently healthy people, is of clinical significance. A comparison can be made between the blood pressures found in the various body build groups and the range of variation of the entire population aged 65 to 106 which has already been published (Master, Lasser and Jaffe[33]). The mean blood pressure found in all males, 65 and over, was 145 mm. Hg systolic and 82 mm. Hg diastolic; in females, it was 156 mm. Hg systolic and 85 mm. Hg diastolic. In the males the middle 80% range ($\pm$ 1.282 δ) was 115 to 175/70 to 95; in the females it was 120 to 192/65 to 102. The middle 95% range ($\pm$ 2 δ) in males was 100 to 190/62 to 102, in females, 100 to 212/55 to 112.

In the underweight of both sexes, the blood pressure is somewhat lower than average (139.5/78.7 in males and 152.3/82 in females); in the severely overweight it is higher than average (151.2/85.6 in males and 159.6/89 in females). However, the degree of deviation from the average is not large and even the severely overweight subjects have blood pressures that fall well within the limits of the middle 80% range. This is due, in part, to the fact that all the subjects were apparently healthy.

This type of analysis tends to minimize the effect of obesity upon blood

pressure, because all persons with cardiovascular disease have been excluded, and the sample tends to be increasingly select. The proportion of obese persons who suffer from hypertensive cardiovascular disease (Master and Jaffe[31]) or coronary artery disease (Master, Jaffe and Chesky[32]), is higher than that in the general population. Had they been included in the sample with the apparently healthy subjects, it is likely that the blood pressure of those in the overweight groups would be considerably higher than that of the subjects in the average or underweight groups, among whom the incidence of these diseases is lower. Such an analysis is now in progress.

Why is the blood pressure higher in overweight subjects than in those who are underweight? It may be that this does not represent a true difference in pressure within the circulatory system, but an artefact caused by the use of a single, standard size, 13 cm. blood pressure cuff for all patients, the accuracy of which is influenced by the circumference of the upper arm (Fletcher[18], Pickering, Fraser Roberts and Sowry[40], Ragan and Bordley[43], Trout, Bertrand and Williams[54] and Wood and Cash[55]). Might the difference disappear if it were possible to measure pressure by direct arterial puncture? There is some evidence that the upper arm circumference varies directly with weight (O'Brien and Shelton[39]). Ragan and Bordley[43] showed that the indirect blood pressure tended to be higher than the direct intraarterial pressure in subjects with large arms, and lower in subjects with small arms. On the basis of scattered observations, they believed that the overestimation of diastolic pressure was 3 mm. Hg for each 1 cm. increase in arm circumference in subjects whose arms were 30 to 42 cm. in circumference. A review of their data shows that these high values appeared only when the arms were of very large circumference, generally more than 38 cm. The available experimental evidence does not seem to us to be sufficiently conclusive to prove that a linear relationship of predictable degree exists between arm circumference and the error resulting from cuff measurements. This, however, may partly explain the difference in the blood pressure between underweight persons and those who are overweight. We do not feel that it accounts for the entire difference, nor that obese, healthy individuals, on an average, have the same true blood pressure as those who are underweight. Other forms of study corroborate our point of view. A thorough survey of the data gathered from insured persons shows that obese adults have a shorter life expectancy, that is, a higher than average age-adjusted mortality rate because of an increased incidence of cardiovascular disease, diabetes and atherosclerosis among them (Dublin[10] and Dublin and Marks[15]). Numerous studies have shown that the incidence of sustained hypertension and hypertensive cardiovascular disease is higher among the obese (Levy *et al.*[26], Master and Oppenheimer[34], Nuzum and Elliott[38] and Short and Johnson[47]). Significant electrocardiographic deviations were found to be seven times more frequent among obese males than among those who were underweight (Armstrong *et al.*[3], and Short[46]). In a study of men who were granted substandard insurance because of overweight, Marks[28] showed that there was a reduced mortality in those who reduced their weight. He reported that the mortality of all the moderately overweight males was 142% of the standard, whereas those who had lost sufficient weight to be given standard insurance had a mortality rate of only

113% of the standard. This reduction in mortality was attributed solely to reduction in weight.

It has been shown that the blood pressure decreases with loss of weight in both average (Keys, Henschel and Taylor[24]) and overweight subjects (Adlersberg, Coler and Laval[1], Bauman[4], Benedict *et al.*[5], Master and Oppenheimer[34], Moschowitz[37], and Terry[51]). In a most carefully controlled study, Fletcher[18] showed that loss of weight resulted in a reduction of the blood pressure, and that the degree of reduction was greater than could possibly be attributed to changes in arm circumference. The degree of hypertension found in obese females was also considerably in excess of that which might have been ascribed to the girth of the arm. It is not unreasonable, therefore, to conclude that obesity does pose a cardiovascular strain, and that excessive weight is associated with a true elevation of the blood pressure even among apparently healthy subjects.

Physiologic studies have demonstrated the nature of the metabolic burden imposed by obesity. Master and Oppenheimer[34] and Prodger and Dennig[42] showed that in the obese, the standard "two-step" exercise resulted in an abnormal elevation of pulse rate and blood pressure, as well as in a decreased work tolerance. These abnormalities reverted to normal after a loss of weight. It has also been shown that obese persons have a higher resting oxygen consumption and an inefficient cardiovascular adjustment to exercise, manifested by a greater oxygen consumption and a higher cardiac output per unit of work performed (Master *et al.*[35] and Taylor, Brozek and Keys[50]). Even though not of striking magnitude, these burdens imposed by obesity ultimately result in cardiovascular complications and a higher mortality rate.

In confirmation of this higher mortality and morbidity, a progressive increase in the proportion of subjects with the underweight body build was noted with advancing age in those people over 65.

The absence of any relationship between the blood pressure and height of subjects over 65 has previously been reported in a study of subjects from 16 to 64 years of age (Master, Dublin and Marks[29]), and by the vast majority of other investigators. Robinson, Brucer and Mass[44] did report that short people have a somewhat higher blood pressure than tall ones, but that the difference was very slight.

All of the observations reported in this study, as well as the findings of the mortality investigations of insurance companies and evidence of the physiological burdens of obesity, clearly show that the life expectancy of the underweight is better than that of the obese.

Summary and Conclusion. A study has been made of the relationship of the blood pressure to height, weight and body build in apparently healthy subjects over the age of 65. The data were gathered by means of questionnaires sent to physicians throughout the country, as part of a study of the blood pressure of the aged. Subjects of each sex were classified into 3 height groups (short, average and tall) and into 4 weight groups within each height group: underweight subjects who were at least 10% lighter than the mean in their height group; average weight subjects who weighed from 9% less to 9% more than the mean in their height group; moderately overweight subjects who weighed more than 10% and less than 25% above the mean in their height group; severely overweight subjects who weighed 25% or more than the mean of their height group.

The blood pressure rises with increasing weight in all height groups in

both sexes, but bears little or no relationship to height alone. The blood pressure is not related to the absolute weight, but rather to the relative weight (body build). The average pressure in underweight males was about 140/79, in average weight males about 145/81 in moderately overweight males about 148/84, and in severely overweight males about 151/85. The average pressure in underweight females was about 151/82, in average weight females about 157/85, in moderately overweight females about 158/86, and in severely overweight females about 160/88.

The clinical significance of the blood pressure variations with body build is discussed, and the general conclusion reached is that obesity reduces the life span, and the outlook for thin people is the most favorable.

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SUMMARIO IN INTERLINGUA

Relation Del Pression Sanguinee Con Peso, Altor, E Conformation Corporee In Apparentemente Normal Subjectos De 65 A 106 Annos De Etate

Ha essite effectuate un studio in re le relation del pression sanguinee con altor, peso, e conformation corporee in apparentemente normal subjectos de plus que 65 annos de etate. Le datos esseva colligite per medio de un questionario inviate a medicos in omne partes del pais como parte de un studio del pression sanguinee in personas de etate avantiate. Le subjectos de ambe sexos esseva classificate in 3 gruppos de altor (curte, intermedie, e grande) e in 4 gruppos de peso intra cata un del gruppos de altor: subjectos a peso insufficiente qui esseva al minus 10% plus leve que le peso median in lor gruppo de altor; subjectos a peso medie qui esseva inter 9% plus leve e 9% plus pesante que le peso median in lor gruppo de altor; subjectos a peso moderatemente excessive qui pesava plus que 10% e minus que 25% plus que le peso median in lor gruppo de altor; e subjectos a peso severmente excessive qui esseva plus que 25% plus pesante que le peso median in lor gruppo de altor.

Le pression de sanguine cresce con pesos crescente in omne gruppos de altor in ambe sexos, sed illo monstra pauc o nulle relation al altor per se. Le pression de sanguine non es relationate al peso absolute sed plus tosto al peso relative (conformation corporee). Le pression medie in masculos de peso insufficiente esseva circa 140/79, in masculos de peso medie circa 145/81, in masculos de peso moderatemente excessive circa 148/84, e in masculos de peso severmente excessive circa 151/85. Le pression medie in femininas de peso insufficiente esseva circa 151/82, in femininas de peso medie circa 157/85, in femininas de peso moderatemente excessive circa 158/86, e in femininas de peso severmente excessive circa 160/88.

Es discutite le signification clinic de variationes del pression sanguinee in correlation con le conformation del corpore. Le conclusion general es que obesitate reduce le longevitate e que le prospectos pro individuos magre es le plus favorabile.

RELATIONSHIP OF THE P WAVE TO LEFT ATRIAL VOLUME IN RHEUMATIC HEART DISEASE WITH MITRAL STENOSIS*

By Louis A. Soloff, M.D.
PROFESSOR OF CLINICAL MEDICINE AND HEAD OF DIVISION OF CARDIOLOGY, TEMPLE UNIVERSITY SCHOOL OF MEDICINE AND HOSPITAL

AND

Jacob Zatuchni, M.D.
ASSISTANT PROFESSOR OF MEDICINE, TEMPLE UNIVERSITY SCHOOL OF MEDICINE AND HOSPITAL; ASSOCIATE IN MEDICINE, EPISCOPAL HOSPITAL

(From the Departments of Medicine, Temple University School of Medicine and Hospital, and Episcopal Hospital, Philadelphia, Pennsylvania)

The P wave is characteristically deformed in some but not all electrocardiograms of persons with rheumatic heart disease and mitral stenosis. Recognition of this change alerts the clinician to the possible presence of mitral stenosis or helps confirm his diagnosis. The pathogenesis of this change, however, is not clear. It has been variously attributed to left atrial disease, left atrial hypertrophy, increased left intra-atrial pressure, left atrial enlargement or various combinations of all four (Berliner and Master[1], Lepeschkin[6], Sodi-Pallares[8], and Trounce[13]). Our purpose, at this time, is to determine the relationship, if any, between these P wave findings and the volume of the left atrium.

Materials and Methods. Twenty persons, 14 females and 6 males, 19 to 59 years of age with rheumatic heart disease, mitral stenosis and normal sinus rhythm were selected at random. The criteria for the diagnosis of isolated mitral stenosis have been described elsewhere (Soloff and Zatuchni[10]). Severe mitral stenosis was found in each of the 10 who had a mitral valvotomy. None of the 20 had any major or minor manifestation of rheumatic activity but 2 of the 10 who had surgery had Aschoff bodies and an additional 2 nonspecific inflammatory changes in the biopsied specimen of the left auricle.

All were studied by the combined techniques of cardiac catheterization and simultaneous biplane stereoscopic angiocardiography described elsewhere (Soloff *et al.*[11]). The method of measuring left atrial volume has also been previously described (Soloff *et al.* [12]). Heart size was determined from conventional teleoroentgenograms and correlated with the internal thoracic diameter in the manner suggested by Hilbish and Morgan[5].

The conventional 12 lead electrocardiogram was taken under basal conditions at normal sensitivity. The recommendations of the New York Heart Association for measurement of amplitude and for descriptive terms were used[3]. The greatest amplitude of P in any bipolar extremity lead is given. The direction and amplitude of each component of a diphasic P is also given. The electric axes of P and QRS were determined by inspection of amplitude and duration.

Results. The results are given in Table 1 and are arranged according to increasing volume of the left atrium.

The volume of the left atrium varied from 192 ml. to 756 ml. Seven did not exceed 300 ml., 5 were between 300 ml. and 400 ml., 6 between 400 ml. and 500 ml., and 2 were greater than 500 ml.

Heart size was within the limits of normal (−25 to +25) in 11, slightly increased (no greater than +35) in 3, moderately increased (no greater than

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TABLE 1.—PERTINENT ELECTROCARDIOGRAPHIC FINDINGS IN PERSONS WITH RHEUMATIC HEART DISEASE AND MITRAL STENOSIS LISTED ACCORDING TO VOLUME OF LEFT ATRIUM

Subject	*Sex*	*Age*	*Left Atrial Volume (ml.)*	*Heart Size (% Deviation) (N = −25 to +25)*	*P Wave Amplitude (mm.)*	*Notching*	*P Wave Duration (sec.)*	*Axis*	V_1	V_2	*qR in* V_1	*QRS Axis*
1. J.P.	F	22	192	+30	2.0	+	0.12	55°	(−2.5)	(+0.5–1)	0	80°
2. M.D.	F	20	206	+20	2.2	+	0.08	30°	(+0.75–1)	(+1)	0	85°
3. P.M.	F	19	216	+15	2.0	0	0.10	0°	(+0.5–0.75)	(+1)	0	62°
4. R.C.	F	35	225	+20	2.0	+	0.12	60°	(+1–1)	(+1.5)	0	25°
5. L.M.	F	45	241	+15	0.75	+	0.08	30°	(+0.5)	(+0.25)	0	55°
6. W.O.	F	33	270	+ 8	2.2	+	0.11	−30°	(+0.25–1)	(+1)	0	85°
7. C.P.	F	32	293	+20	2.5	0	0.08	60°	(+0.25–0.5)	(+1)	0	30°
8. M.T.	F	39	308	+48	2.0	+	0.12	30°	(+3)	(+6)	0	100°
9. G.I.	F	37	322	+32	4.0	+	0.12	75°	(+1.8–2)	(+2)	+	100°
10. J.L.	M	29	335	+60	2.0	+	0.12	65°	(+1–2)	(+1.2)	+	90°
11. L.S.	F	42	345	− 2	2.7	0	0.10	58°	(+0.75)	(+0.5)	0	50°
12. J.S.	F	59	360	+38	1.7	0	0.08	90°	(+0.75–1)	(+1–1)	0	75°
13. M.H.	F	25	416	+27	2.0	+	0.12	60°	(+0.5–1)	(+1–1.2)	0	100°
14. A.V.	M	31	420	+20	1.8	+	0.12	60°	(+1.2–1.4)	(+0.5–1)	0	45°
15. C.S.	F	37	421	+20	1.3	0	0.08	75°	(+1–1)	(+1–1)	0	75°
16. G.G.	M	41	433	+42	2.2	+	0.12	75°	(+1.2–1.7)	(+0.75–1.2)	0	90°
17. C.M.	M	41	440	+20	1.0	+	0.12	60°	(+1–1)	(+1–1)	0	62°
18. M.G.	F	31	480	+40	2.0	+	0.12	60°	(+0.5–1)	(+1–0.2)	0	80°
19. A.M.	M	41	520	+ 8	2.0	0	0.12	60°	(−1.8)	(−1.4)	0	90°
20. T.J.	M	48	756	+60	1.7	+	0.12	30°	(+0.75–2)	(+2.2–1)	+	90°

+45) in 3, and greatly increased (more than +45) in 3.

The amplitude of P in the extremity leads varied from 0.75 mm. to 4.0 mm. It was 1.8 mm. or less in 6, 2.0 mm. in 8, 2.2 mm. in 3, 2.5 mm. in one, 2.7 mm. in one, and 4.0 mm. in the remaining one.

A left atrial volume of 241 ml. was present in the one with a P amplitude of 0.75 mm. and of 322 ml. in the one whose P amplitude was 4.0 mm.

The left atrial volume varied from 192 ml. to 520 ml., (average 337 ml.), in the 8 with a P amplitude of 2.0 mm. Five of the 8 had increased heart size.

The left atrial volume varied from 241 ml. to 756 ml. (average 440 ml.), in the 6 with a P amplitude less than 2.0 mm. Two of the 7 had increased heart size.

The left atrial volume varied from 206 ml. to 433 ml., (average 312 ml.) in the 6 with a P amplitude greater than 2.0 mm. Two of the 5 had increased heart size.

The electric axis of P varied from −30° to +90°. It was vertical (+75° to+90°) in 4, semivertical (+45° to +74°) in 10, intermediate (+16° to +44°) in 4, horizontal (−30°) in one and semihorizontal (0°) in one.

The left atrial volume varied from 192 ml. to 520 ml., (average 367 ml.), in the 10 with a semivertical electrical axis of P, from 322 ml. to 433 ml., (average 384 ml.), in the 4 with a vertical axis and from 206 ml. to 756 ml., (average 378 ml.) in the 4 with an intermediate axis. The left atrial volume was 270 ml. in the one with a horizontal axis and 216 ml. in the one with a semihorizontal axis of P.

The electrical axis of QRS was vertical (+75° or more) in 13, semivertical (+45° to +74°) in 5 and intermediate (+16° to +44°) in 2. Increased heart size was present only in those with a vertical electric axis of QRS and was found in 9 of these 14.

The left atrial volume varied from 192 ml. to 756 ml., (average 386 ml.) in those with a vertical electric axis of QRS, from 216 ml. to 440 ml., (average 333 ml.) in those with a semivertical axis, and 225 ml. and 293 ml., (average 259 ml.), in the 2 with an intermediate axis.

Of the 13 with a vertical electric axis of QRS, the P axis was vertical in 4, semivertical in 5, intermediate in 3 and horizontal in one. Heart size was increased in 3 of 4 with vertical P and QRS axes, in 4 of 5 with semivertical P and vertical QRS axes, and in 2 of 3 with intermediate P and vertical QRS axes. The left atrial volume varied from 322 ml. to 433 ml., (average 384 ml.), in those with vertical QRS and P axis, from 192 ml. to 520 ml. (average 389 ml.), in those with vertical QRS and semivertical P axes, and from 206 ml. to 756 ml., (average 423 ml.), in those with vertical QRS and intermediate P axes. Lastly, in the one with a horizontal P and a vertical QRS axis, the left atrial volume was 270 ml. and heart size was not increased.

Of the 5 with a semivertical electric axis of QRS, the P axis was vertical in one, semivertical in 2, intermediate in one and semihorizontal in the remaining one. The left atrial volume was 345 ml. and 420 ml., (average 383 ml.), in the 2 with a semivertical QRS and P axis, 241 ml. in the one with an intermediate P axis, 216 ml. in the one with a semihorizontal P axis and 440 ml. in the one with a vertical P axis. In the 2 with an intermediate QRS axis, the P was also intermediate and left atrial volume was 225 ml. and 293 ml., (average 259 ml.).

Notching of the P wave was a lone finding twice in lead 1 with left atrial volumes of 241 ml. and 433 ml. and increased heart size in one, once in lead

3 with a left atrial volume of 420 ml. and normal heart size, and never occurred as a lone finding in lead 2 or any augmented unipolar or precordial lead.

Notching of P occurred in variable combinations of leads in 11 of the 20. Seven of these 11 were notched in lead 1 with left atrial volumes between 192 ml. and 756 ml., (average 374 ml.), and increased heart size in 4. Four were notched in lead 3 with left atrial volumes between 192 ml. and 480 ml. (average 434 ml.), and increased heart size in 3. Six were notched in lead aVR with left atrial volumes between 192 ml. and 756 ml. (average 386 ml.), and increased heart size in 4. Two were notched in lead aVL with left atrial volumes of 192 ml. and 225 ml. and increased heart size in one. Five were notched in lead aVF with left atrial volumes between 192 ml. and 480 ml. (average 323 ml.), and increased heart size in all.

Eight different combinations of extremity leads showed notching, with leads 1, 2 and aVR the maximum number of leads in a combination. There was no relation, however, between any combination and the volume of the left atrium. Similarly, the number of precordial leads which showed notching of the P wave was not related either to the degree of left atrial enlargement, which varied from 192 ml. to 440 ml. (average 309 ml.), or to heart size which was increased in 2.

Duration of the P wave varied from 0.08 to 0.12 second. In 12 of the 20, it was 0.12 second and the left atrial volume varied from 192 ml. to 756 ml. (average 404 ml.). All but one with a left atrial volume greater than 400 ml. had a duration of P of 0.12 second whereas only 5 of 12 with a smaller left atrial volume had such duration. In the 4 with specific or nonspecific inflammatory changes in the biopsied specimen of the left auricle whose left atrial volume was between 192 ml. and 520 ml. (average 387 ml.), the duration of P was also 0.12 second.

In lead V_1, the P wave was positive in 3 with an amplitude of 0.5 mm., 3.0 mm. and 0.75 mm. The left atrial volume was 241 ml., 308 ml., and 345 ml. respectively. Heart size was increased in one. The P was diphasic (+ −) in 15. The greatest positivity was 2.0 mm. and the greatest negativity also 2.0 mm. The left atrial volume varied from 206 ml. to 756 ml. (average 373 ml.), and heart size was increased in 7. Lastly, the P wave in lead V_1 was entirely negative in 2 (−1.8 mm. and −2.5 mm.). In these 2, the left atrial volume was 520 ml. and 192 ml. respectively and heart size was increased only in the latter.

A qR complex was found in lead V_1 in 3. The heart size was increased in all and in 2 there was electrocardiographic evidence of right ventricular hypertrophy in the precordial leads. All 3 had rightward deviation of the QRS axis. The left atrial volume was 322 ml., 335 ml., and 756 ml. respectively.

Discussion. Our 20 cases, selected at random, are representative of rheumatic heart disease with clinically "pure" mitral stenosis and sinus rhythm, as indicated by the fact that the volume of the left atrium was predominantly less than 500 ml. We have shown elsewhere that as the left atrial volume increases, the incidence of mitral regurgitation and atrial fibrillation increases[10].

The P wave displayed some abnormality in at least one lead in all instances. It was broad or notched or increased in amplitude or diphasic in leads V_1 and V_2 or its axis was deviated to the left. The unlikely association of entirely normal P waves with severe mitral stenosis has been recently reemphasized by Fraser and Turner[4].

Notching was the commonest abnormality, which confirms the findings of Berliner and Master[1] and of Fraser and Turner[4]. It was most commonly seen in Lead 1 and was never a sole finding in lead 2 or the unipolar extremity or precordial leads.

The nature of notching was recently elucidated by Reynolds[7]. In a study based upon atrial electrograms taken at the time of mitral valvotomy, he showed that the P wave in the electrocardiogram is actually a summation of both right and left atrial contractions and that notching occurred when the atria did not contract simultaneously. He stated that asynchrony of atrial contraction may be due to differences in time of contraction, to delay in conduction either within or between atria, or to increased atrial size.

It appears that increased size of the left atrium is an important factor in the production of notching. Not only is notching frequently found with enlargement of the left atrium in mitral stenosis but we have also noted, as have others (Berliner and Master[1], New York Heart Association[3]), the occurrence of notching in conditions other than mitral stenosis associated with left atrial enlargement. The effect of left atrial enlargement alone, however, may be a limited one because the frequency of notching, its extent or degree, could not be correlated with the degree of enlargement of the left atrium. Conversely, notching may be absent in enlargement of the left atrium even of moderate degree.

Notching may also be related to atrial conduction velocity as measured by the duration of the P wave in the electrocardiogram. If a duration of less than 0.12 second is accepted as normal, as suggested by Bradley and Marriott[2], 5 of 8 cases with normal duration of P and 11 of 12 with prolonged duration had notching. Hence, conduction velocity is related better to notching than is left atrial volume. However, as with the finding of notching, conduction velocity did not progressively increase with increased volume of the left atrium, for, although the duration of P was less than 0.12 second in only one of 8 cases with a left atrial volume greater than 400 ml., it was similarly prolonged in 5 of 12 cases with a smaller left atrium and did not get longer with a larger left atrium.

Prolongation of conduction velocity is not the only mechanism whereby notching may be produced. Indeed, notching was found in 3 cases with normal duration of P. But it is unquestionably a very important factor for only one of 12 cases with prolonged duration of P did not show notching.

The significant but limited influence of left atrial enlargement in the production of either notching or prolonged duration of the P wave suggests the possible additional role of myocardial changes independent of left atrial enlargement. Indeed, all 4 with inflammatory changes in the left auricle had prolonged duration of P. Such effect may be mediated by increasing asynchronism, as suggested by Reynolds[7], or by change in conduction path, either in duration or in route. Indeed, Reynolds[7] found that where asynchronism was greatest, myocardial factors rather than enlargement of the left atrium were dominant. In such instances, the voltage of the P wave tended to be low and the heart large.

Only 4 of our 20 patients had an amplitude of P greater than normal, judged by the criterion of the New York Heart Association[3]. High amplitude was also a rare finding in Berliner and Master's series[1]. These investigators sought reasons other than uncomplicated mitral stenosis to explain high amplitude, such as enlargement of both atria, but Fraser and Turner[4] were

unable to establish a relation between tall, spiked P waves and the size of the right atrium, the degree of pulmonary hypertension or of right ventricular hypertrophy. It has been frequently documented that sudden failure of either ventricle may produce immediate but not necessarily sustained increase in amplitude of P.

For any given amplitude of P, the left atrial volume varied greatly, regardless of similarity of heart size. Moreover, although the average left atrial volume was greatest in those with an amplitude of P less than 2.0 mm. and least in those exceeding 2.0 mm., no statistically significant differences were found.

Perhaps the discrepancy of amplitude of P and left atrial volume is related to shift in electric axis. It is conceivable that with increase in left atrial volume, the P vector shifts increasingly away from the frontal plane. However, we were unable to find such a shift. Any degree of shift, if it occurs at all, must be small, for although the P waves in leads V_1 and V_2 were diphasic more frequently than in the normal, both were rarely negative. Moreover, the occurrence of negative P waves in these leads could be explained by rightward deviation of the electric axis of P. Amplitude also could not be related to the electric axis of P. The electric axis of P was usually semivertical, occasionally vertical and rarely horizontal or semihorizontal. This was surprising, for we had anticipated a rather frequent occurrence of left axis deviation of P, a finding said to be characteristic of the P mitral pattern. Left axis deviation of P was not associated with larger left atrial volumes. To the contrary, the average left atrial volume was larger with right axis deviation. But there was no statistically significant correlation between the electrical axis of P and the degree of left atrial enlargement nor could we correlate this axis with the pulmonary artery or capillary pressures or the difference between them.

The shift of P appeared related best to the electric axis of QRS. As with rightward deviation of P, deviation of QRS to the right was also associated with larger left atrial volumes. But such deviation of QRS rather than that of P appeared to have a better chance of correlation with the degree of left atrial enlargement, for in those with a similar QRS axis, the left atrial volume tended to be smaller as P deviated more either to the right or to the left. Again, however, no statistical significance could be obtained between the electric axis of QRS and the volume of the left atrium, regardless of the electric axis of P.

All of the 9 with enlarged hearts had a QRS axis of $+75^\circ$ or more. In these 9, the left atrial volume varied from 192 ml. to 756 ml. and the amplitude of P from 1.7 mm. to 4.0 mm. Only 2 were less than 2.0 mm. and both of these were actually 1.7 mm. Amplitudes lower than this were found in 3 persons who had normal heart size. Moreover, those with a lower voltage of P did not show any significant differences from those with a higher voltage in the results of the angiocardiographic circulation times. It is for these reasons that we cannot agree with Reynolds' interesting suggestion that a large P wave may indicate little enlargement of the heart and good functioning myocardium and a low P wave a large heart and poorly functioning myocardium.

Finally, attention should be directed to the finding of a qR complex in lead V_1. Sodi-Pallares, Bisteni and Herrman[9] insist that such a finding in the absence of myocardial infarction depends upon enlargement of the right atrium. Three

of our 20 cases had a qR in lead V_1. This finding could not be correlated with degree of left atrial enlargement. Heart size was always increased, the right atrium as visualized by angiocardiography was enlarged and marked pulmonary hypertension was present.

Summary and Conclusions. 1. The relationship of the character of the P wave to the volume of the left atrium was studied in 20 persons with rheumatic heart disease, mitral stenosis and normal sinus rhythm.

2. Notching of the P wave was the commonest abnormality and high amplitude the least frequent.

3. Notching, amplitude or duration of the P wave could not be correlated with degree of left atrial enlargement.

4. Electric axis of P was commonly semivertical, occasionally vertical and rarely horizontal.

5. A qR complex in lead V_1 is not related to degree of left atrial enlargement but is associated with marked pulmonary hypertension, right atrial enlargement and increased heart size.

6. There is a tendency for the large left atria to be associated with rightward deviation of P, but left atrial volume is best correlated, although poorly, with rightward deviation of QRS associated with an almost equal rightward deviation of P.

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(Interlingua on page 277)

A DOUBLE-BLIND METHOD FOR EVALUATING ANALGESICS IN MAN

By Richard I. H. Wang, Ph.D., M.D.
RESIDENT IN MEDICINE

AND

Charles M. Gruber, Jr., M.D., D.Sc. (Med.)
RESEARCH PHYSICIAN

(From Indianapolis General Hospital and Lilly Laboratory for Clinical Research, Indianapolis, Indiana)

Houde and Wallenstein have on several occasions reported the results of experiments comparing various analgesic agents. Gruber *et al.*[2] compared a method they had devised for testing analgesic drugs to the one reported by Houde and Wallenstein. Both methods used patients with pain or discomfort produced by chronic disease; both methods supplied reliable estimates of analgesic activity. The method of Houde and Wallenstein required that patients be interrogated at hourly intervals for 6 hours. This was time consuming, but data were accumulated rapidly. These data allowed accurate estimates of analgesic activity with a small number of patient days. Also, these hourly visits permitted the determination of the duration of analgesic activity. The modification of their method called for single daily visits by the investigator. Data were obtained more slowly and the durations of actions of the drugs could not be determined.

In this report a second modification of the method of Houde and Wallenstein is introduced. Two analgesic drugs, meperidine hydrochloride (Demerol) and dextro propoxyphene hydrochloride (Darvon) were chosen for the evaluation of the method. Dextro propoxyphene is a new non-narcotic analgesic with a potency and duration of effectiveness equivalent to that of codeine (Gruber *et al.*[2]).

Materials and Methods. The medications were given orally in equal numbers of identically appearing capsules. These capsules contained cornstarch, 50 mg. of meperidine or 65 mg. of dextro propoxyphene. The analgesics were administered in multiples of these recommended clinical doses. The number of capsules was constant during each 24-hour period.

The analgesics were administered orally at noon and midnight. At 6:00 p.m. and 6:00 a.m., blank capsules were given. The medications were coded with serial numbers (1 to 20) and were given in numerical order. The first experimental analgesic was always administered at noon of the first day. Each night at midnight, the medication was changed to the other analgesic.

Seven patients who were thought to have severe pain were admitted to a research ward for these tests. The diagnoses of these patients were herniated nucleus pulposis (2), multiple myeloma (2), rheumatoid arthritis, disseminated lupus erythematosus, and herpes zoster. The testing procedure was carefully explained to the patients prior to the experiment. The patients were visited every 2 hours by registered nurses. Without questioning the patient, the nurse placed a 10 × 4 inch board before the patient. Nine holes had been drilled part way through this board. The holes were numbered from zero to eight, so that 0, 2, 4, 6, and 8 corresponded to "none, slight, moderate, severe, and agony" respectively. A peg was given to the patient who placed it in the hole most closely representing the severity of pain present at that moment. The nurse recorded the number of that hole on a score sheet.

TABLE 1.—A SUMMARY OF THE RESULTS OBTAINED BY QUESTIONING PATIENTS AT 2-HOUR INTERVALS, DAY AND NIGHT FOR 5 DAYS. THE SUM OF THE PAIN SCORES FOR EACH PATIENT ARE PRESENTED IN THE BODY OF THE TABLE. AT THE SIXTH HOUR, BLANK CAPSULES WERE GIVEN

Patient Number	*First Medication*	*Capsules per Dose*	*Hours after Dextro Propoxyphene*								*Hours after Meperidine*								*Total*
			0	*2*	*4*	*6*	*8*	*10*	*12*	*T*	*0*	*2*	*4*	*6*	*8*	*10*	*12*	*T*	
1	Propoxyphene	4–6	31	23	30	34	31	30	35	214	34	24	26	30	30	29	28	201	415
2	Meperidine	4	12	12	12	13	14	12	10	85	14	15	14	14	14	14	12	97	182
3	Propoxyphene	4	37	33	32	32	32	35	36	237	33	27	28	30	30	31	33	212	449
4	Propoxyphene	4	24	10	12	26	24	16	22	134	20	11	18	15	14	18	22	118	252
5	Meperidine	4	21	11	12	15	16	19	26	120	26	24	15	16	24	20	19	144	264
6	Propoxyphene	4–6	20	12	10	12	9	6	10	79	13	9	9	11	8	13	15	78	157
7	Meperidine	6	20	18	16	18	16	14	20	122	22	16	14	18	16	16	16	118	240
										991								968	
	Total		165	119	124	150	142	132	159		162	126	124	134	136	141	145		1,959

Results. Four hundred and ninety estimates of pain or discomfort were available for analysis. The total scores for each of the 7 patients are presented in Table 1. Analysis of the data in Table 1 is presented in Table 2.

TABLE 2.—ANALYSIS OF VARIANCE OF DATA IN TABLE 1

Source	*Sum of Squares*	*df*	*Mean Square*
Patients (P)	5297	6	883‡
Drugs (D)	5	1	5
Hours (H)	365	6	61‡
Analgesics (2,4,6) vs. Blanks (8,10,12)	(72)	(1)	72‡
Interactions*	486	48	10
PxD	(123)	(6)	21
PxH	(324)	(36)	9
DxH	(39)	(6)	7
Remainder†	324	36	9
Total	6477	97	

*Error term for main effects
†Error term for primary interactions
‡Significant at p less than 0.01

The patients, days, and hours were sources of significant variance from a random effect. The sum of the effects of the analgesics at 2, 4, and 6 hours differed from the sum of the effects of the placebos at 8, 10 and 12 hours. This was a source of significant variance (p less than 0.01). No difference between the effectiveness of the 2 analgesics at these doses was demonstrated. Tests for the presence of significant primary interactions indicated that the patients did not respond differently to the 2 analgesics.

Discussion. There are 4 general methods now in use for studying the degree of effectiveness of analgesic agents. These are: (1) testing the effects of the agents upon the reaction of animals to noxious stimuli; (2) the measurement of pain threshold-raising effects in trained normal human subjects; (3) the measurement of the pain reducing effects of the agents in patients or in normal humans with experimentally induced pain; and (4) the analysis of reports from patients with pain produced by disease concerning "comfort" after the administration of the medications. Analyzing patients' reports of "comfort" is unquestionably the best available method for assaying the over-all effectiveness of an analgesic in the relief of suffering. At the same time, any untoward side reactions produced by the agents may be evaluated (Hardy, Wolff and Goodell[3]). Techniques involving induced pain are of value but fail to measure the effectiveness of analgesia in pain produced by disease.

Patients with chronic pain are preferable to patients with pain from acute disease since the former experience a more constant degree of discomfort. These patients may be given each of several medications without any appreciable change in their basic pain status. Continuous observation (day and night) shortens the lapse of time involved in the study and thus diminishes the alterations in the basic pain status.

In this study it is shown that the relief of discomfort was significantly better with the analgesics used than with the identical blank medications. No significant difference in the efficacy of the two analgesics was observed.

Summary. (1) A double-blind clinical method of evaluating the analgesic activities was described.

(2) Dextro propoxyphene and meperidine were shown in this study to be effective oral analgesics.

(3) Patients with severe pain obtained approximately the same relief from pain or discomfort with 260 mg. of dextro propoxyphene as they did from 200 mg. of meperidine.

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SUMMARIO IN INTERLINGUA

Un Methodo "Bis-Occulte" Pro Evalutar Analgesicos In Humanos

1. Es describite un methodo "bis-occulte" pro evalutar activitates analgesic.

2. Esseva monstrate in iste studio que dextro-propoxypheno e meperidina es efficace analgesicos oral.

3. Patientes con sever grados de dolor obteneva approximativemente le mesme alleviamento per medio de 260 mg de dextro-propoxypheno como per medio de 200 mg de meperidina.

SUMMARIO IN INTERLINGUA

(See page 301 for original article)

Correlation Electroencephalographic De Accessos De Riso

1. Quatro juveniles con non-motivate accessos epileptic de riso esseva studiate electroencephalographicamente. Le diagnoses clinic esseva le sequente: (1) Papilloma del tertie ventriculo con infiltration in le extremitate del lobo temporal. (2) Convulsiones mesencephalic postencephalitic. (3) "Trauma de nascentia" con retardo mental e convulsiones acinetico-motori e de lobo temporal. (4) "Trauma de nascentia" con hypercinetic disordine de comportamento e nocturne accessos de riso.

2. Le natura epileptic de iste accessos de riso esseva demonstrate per le facto que illos esseva incongrue con omne factor ambiental, que illos precedeva o se manifestava como parte de altere phenomenos epileptic, e que omne le 4 subjectos habeva anormalitates paroxysmal in le electroencephalogramma.

3. Electroencephalogrammas obtenite durante le intervallos inter le convulsiones exhibiva un extense varietate de anormalitates, per exemplo formation de puncta temporal focal, formation del variante puncta-domo, e retardo diffuse (in un patiente, post intervention neurochirurgic non sequite per discontinuation del accessos de riso). In 2 patientes, registrationes electroencephalographic esseva obtenite durante accessos de riso, e ambes esseva characterisate per discargas focal de lobo temporal.

4. Un revista del litteratura rende evidente que accessos de riso tende a occurrer in disturbationes del areas del tertie ventriculo e del diencephalo con projection al lobo temporal. Nostre proprie experientias electroencephalographic e neurologic indica le possibilitate que activation del area limbic es responsabile pro epileptic accessos de riso.

ELECTROENCEPHALOGRAPHIC CORRELATION OF LAUGHING FITS*

By André A. Weil, M.D.

DEPARTMENT OF NEUROLOGY, WESTERN RESERVE UNIVERSITY MEDICAL SCHOOL (CITY HOSPITAL, CLEVELAND); DEPARTMENT OF NEUROLOGY AND PSYCHIATRY, HURON ROAD HOSPITAL, EAST CLEVELAND, OHIO

William A. Nosik, M.D.

DEPARTMENT OF NEUROSURGERY, HURON ROAD HOSPITAL; ST. LUKE'S HOSPITAL; AND UNIVERSITY HOSPITALS, CLEVELAND, OHIO

AND

Nicholas Demmy, M.D.

CLEVELAND REGIONAL TREATMENT CENTER AND DEPARTMENT OF NEUROLOGY, HURON ROAD HOSPITAL, EAST CLEVELAND, OHIO

Gowers[8] first described laughter following petit mal seizures (1881). The French physician Féré[4,5] was the first one to connect this phenomenon with neuropathological lesions, describing pathological, paroxysmal laughter in 2 patients preceding hemiplegic attacks (1898). We find from then on sporadic reports in the literature mentioning unmotivated laughter or paroxysmal laughing fits as a symptom of a variety of organic brain disorders. The occurrence of forced laughter (in addition to crying and weeping attacks) in pseudobulbar palsy, disseminated sclerosis and amyotrophic lateral sclerosis is well known (Martin[11], Wilson[16]). Unmotivated paroxysmal laughing attacks as part of an epileptic aura or seizure, or both, are somewhat different (Jewesbury[9], Gibbs and Gibbs[7]).

The literature is sparse, indeed, concerning electroencephalographic correlation of these laughing fits. Gibbs and Gibbs[7] describe 14 and 6/sec. positive spikes (thalamic and subthalamic) in 4 patients, an anterior temporal focus in one subject.

In a recent publication, Druckman and Chao[3] observed laughing fits in connection with head nodding attacks, massive spasms and diencephalic seizures in 11 children. Children with massive spasms showed hypsarrhythmias most frequently. The others had slow dysrhythmias, multiple foci of spike discharges, and one patient showed 14 and 6/sec. positive spike paroxysms. Daly and Mulder[2] observed paroxysmal laughter in 2 patients. One patient had an infiltrating tumor in the left temporo-occipital area, the electroencephalogram showing irregular slow waves and occasional fast spikes arising from the posterior portion of the left hemisphere. At times there were, bilaterally, synchronous 4/sec. paroxysms. Their second case had seizures of undetermined etiology; laughing attacks could be produced by Metrazol activation. The sleep EEG showed slow waves in the left temporal region. This rather sparse review makes it apparent that EEG abnormalities connected with laughing fits seem to implicate disturbances pertaining to subthalamic-diencephalic or temporal lobe structures, or both.

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Case Reports. CASE 1. K.R., a 4-year-old male child, had retarded psychomotor development from the time of birth. Three months prior to neurological consultation he developed atonic seizures, at first initiated by getting "limp," consensual eye turning to the left and vomiting. After an attack there was lethargy and sleep. Originally the attacks lasted only one minute and were not accompanied by any tonic-clonic dyskinesias. Two months later his seizures were initiated by "hysterical laughing" and episodes of "fear." One month afterward he started to have tonic-clonic convulsions, again initiated by laughing fits and eye turning to the left. He became more and more hyperkinetic.

The original neurological examination showed a hyperkinetic youngster with some expressive aphasia. The optic discs were full and there was some engorgement of retinal veins. He dragged his right leg somewhat. He had an equivocal Babinski sign on the right and definite Babinski, Chaddock and Oppenheim signs on the left.

In the initial EEG (March 21, 1955) we noted slow spikes and accentuation of delta activity over the left temporal-parietal linkage during waking stages (Fig. 1*A*). During light, natural sleep, focal slow activity, maximal over all *left* temporal and parietal linkages was noted. Sharp spikes (200 μV plus) were noticed coming from the left temporal-parietal electrode derivation predominantly (Fig. 1*B*).

The child was hospitalized. The spinal fluid findings were not remarkable, but the pneumoencephalogram revealed a tumor mass in the floor of the third ventricle, producing a filling defect of considerable size in this ventricle. The mass protruded into the lateral horn on the left, displacing the temporal horn laterally. Arteriograms showed some elevation of the left temporal artery as well as of the first portion of the anterior choroidal artery.

A craniotomy was subsequently performed on April 4, 1955, and proved the existence of a mass arising from the third ventricle and extending into the tip of the left temporal lobe. Neuropathological diagnosis was papilloma of the choroid plexus. Subsequently the child was irradiated with apparent improvement at first. However, "laughing spells" as well as aphasic disturbances recurred, followed by akinetic and an occasional clonic seizure. Anticonvulsant medication ameliorated his laughing spells, but his paroxysmal hyperkinesia increased to such an extent that he had to be transferred to a state school.

We obtained a repeat EEG on June 23, 1956, which showed slow activity in the theta range and only slight accentuation of left temporal slow activity (Fig. 1*C*).

CASE 2. R.J., an 8-year-old, white male child, developed night terrors with visual hallucinations following a severe bout of measles at the age of 4 years. Subsequently he became hyperkinetic and about 3½ months following his initial bout of measles, he developed attacks of "staring into space" and assumed "frozen bodily positions." He had one grand mal convulsion. A local practitioner prescribed anticonvulsant medication and the patient developed laughing fits instead of his "frozen attacks." During these seizures the head turned to the left, chewing movements occurred and his left eyelid drooped. The laughing was explosive and not connected with any environmental stimuli. The initial neurological examination showed hyperkinesia, definite left central facial weakness and accentuation of all deep tendon reflexes on the left.

The first EEG (January 17, 1957) showed 3/sec. slow spike paroxysms (200 μV), occasionally with "ascending" interpolated sharp spike volleys which gave these paroxysms an appearance of abortive spike-dome variant contours. We noted a definite, persistent out-of-phase relationship over the right temporal area and occasionally over the right parietal area, doubtlessly denoting some sort of "spread." At the beginning of hyperventilation a laughing fit occurred which corresponded electroencephalographically with high voltage sharp delta patterns (300 μV) and right temporal phase reversal (Fig. 2*A*).

Neurological observations in the hospital showed normal cerebrospinal fluid dynamics, 14 lymphocytes in the spinal fluid and 44 mg. per 100 ml. protein. Colloidal gold showed a 1-1-2-2-1-1-0-0-0-0 curve. Blood studies showed a slight leukocytosis (13,000). Blood chemistry showed a slightly increased phosphorus level (5.4 mg. per 100 ml.). A pneumoencephalogram (courtesy of Dr. Edward Shannon) showed the ventricles to be normal in size and contour, although there was a minimal degree of asymmetry; the right ventricle was slightly more prominent than the left. Hospital discharge diagnosis was postencephalitic epilepsy associated with laughing fits and right temporal lobe seizures.

The patient was placed on Milontin and Dilantin medication and the laughing seizures ceased. His hyperkinesis was less marked, but he developed "blinking attacks," "head shaking" and "head turning" attacks.

Repeat EEG on May 28, 1957, showed an increase of lengthy 4/sec. hump wave and sharp wave paroxysms (frequently dicrotic)

compared with the previous EEG. The slow waves still reversed over the right temporal area predominantly (Fig. 2*B*).

CASE 3. T.J., an 11-year-old boy, developed "laughing fits" at the age of 7 months! There was some possible trauma at birth, since the baby was "held back." His development was characterized by some psychomotor retardation. He developed akinetic motor seizures at the age of 6½ years. Paroxysmally he was enuretic, overactive and irritable. The initial neurological examination showed hyperactive left patellar reflex and some slight ataxia on the left finger to nose test. A pneumoencephalogram showed no significant abnormalities. Eventually he developed temporal lobe seizures, characterized by chewing and deglutition movements as well as flexion of the right arm. "Giggling" frequently initiated such a seizure, but also occurred independently without a recognizable "seizure" afterward. Laughing fits without cause or reason were observed.

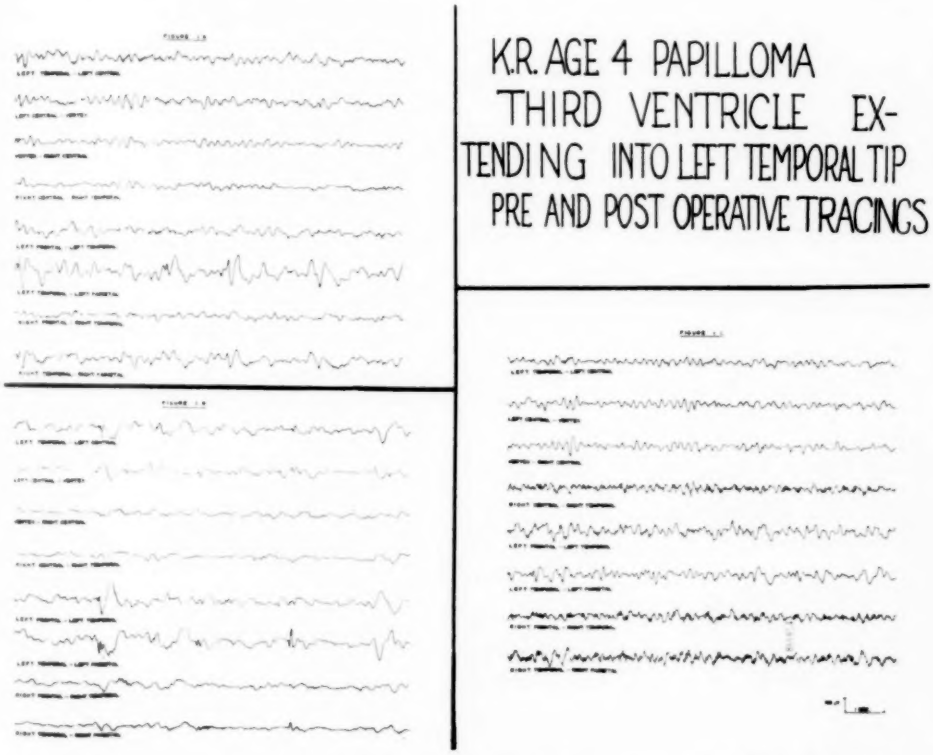

Fig. 1*A*.—3/21/55. Preoperative EEG during waking state: Slow spikes and random delta activity left temporal-parietal electrode derivation.

Fig. 1*B*.—3/21/55. Preoperative, light natural sleep EEG: Focal slow activity, maximal over all left temporal linkages; sharp spikes predominantly in left temporal-parietal electrode derivation.

Fig. 1*C*.—6/23/56. Postoperative EEG during waking state: Dissociated and diffuse slow activity in the theta range. Only slight left temporal-parietal slow wave accentuation.

During a resting EEG (May 25, 1957) we observed very typical petit mal variant bursts (Fig. 3*A*). Occasionally we also noted high voltage delta bursts (300 μV) reversing over the right temporal area. As the record progressed the patient had a typical temporal lobe seizure, initiated by giggling and followed by chewing and deglutition movements as well as flexion of the right arm. The elec-

troencephalographic correlation consisted of a slow spike activity arising from the left temporal area (Fig. 3*B*).

CASE 4. R.R., a 7-year-old male child, was delivered as breech presentation. Overactivity, thermolability and behavior fluctuations persisted from infancy. The mother describes the boy's "laughing attacks" as appearing only at night, sometimes lasting for hours. These were followed by "a daze" and occasionally by enuresis. Attacks occurred at about 2-week intervals. The Stanford-Binet (Form L) test indicated an I.Q. of 89 with "scatter" in the testing (courtesy of Dr. Wilmot Schneider). The referring physician did not notice any definite neurological disturbances except for OS eye muscle imbalance, near vision OS reduced to 20/40 and possible

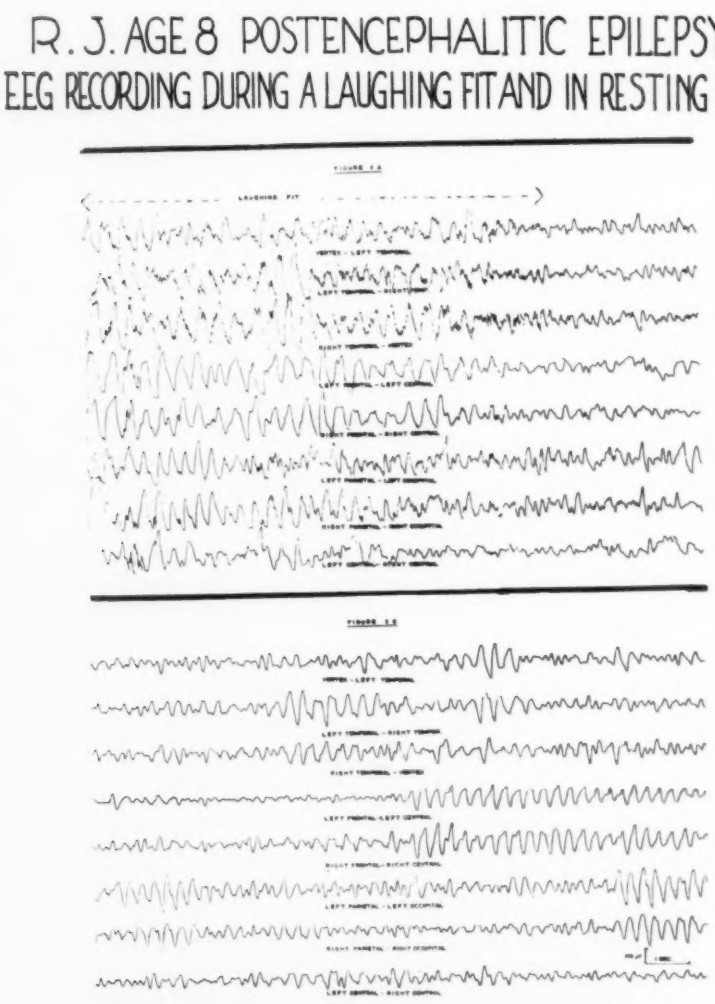

Fig. 2*A*.—1/17/57. Laughing fit electroencephalographically recorded (dotted line). Tracing shows high voltage (300 μV) sharp delta patterns with right temporal phase reversal during attack.

Fig. 2*B*.—5/24/57. Resting pattern, 4/sec. hump wave and sharp wave paroxysms. There are still some phase reversal over the right temporal area and some dicrotic wave contours from the right fronto-central derivation.

astigmatism. There were episodes of transfrontal headaches and abdominal pains. Dilantin Infatabs greatly ameliorated his overactivity and abolished his "laughing attacks."

An electroencephalogram was obtained on June 17, 1957. The resting record showed 7.5/sec. background activity with dicrotic 3.5/sec. hump wave paroxysms interspersed. These were noticeable mainly over the left temporal area, but were also seen over the right temporal and right parietal leads. The left temporal area occasionally showed double spikes of 75 μV output also. During light, natural sleep slow spikes appeared in isolated fashion and in brief volleys, bilaterally asynchronous. These were noticeable mainly over both occipital-parietal and central-temporal linkages (Fig. 4).

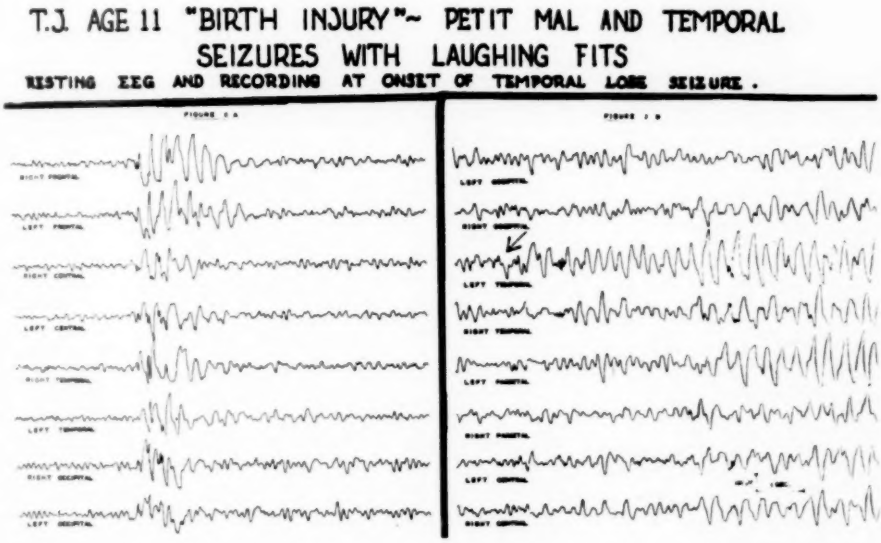
T.J. AGE 11 "BIRTH INJURY"~ PETIT MAL AND TEMPORAL SEIZURES WITH LAUGHING FITS
RESTING EEG AND RECORDING AT ONSET OF TEMPORAL LOBE SEIZURE.

Fig. 3*A*.—5/25/57. EEG during resting states: Typical petit mal variant burst.
Fig. 3*B*.—5/25/57. Record obtained at beginning of typical temporal lobe seizure (see arrow), initiated by giggling and followed by chewing movement, mastication and flexion movements of right arm. The slow spike activity seems to start from the left temporal area. (All leads recorded against a "relative, indifferent" electrode.)

Discussion. Clinical and EEG observations of these 4 cases leave little doubt that laughing fits as described in our patients were epileptic phenomena. Some of these seizures seemed to indicate an epileptic aura (patients K.R. and T.J.); others appeared to be prolonged ictal phenomena (patient R.R.). In one case (patient R.J.) laughing fits occurred both as an epileptic prodrome and during temporal lobe seizures. These epileptic laughing fits are not much different in their basic paroxysmal nature from the episodes of ictal fear and depression described by one of us in two previous communications (Weil 1955[14], 1956[15]) and which occurred as an epileptic aura or ictus. However, some of our "depressive fits" were post-ictal phenomena which were not observed in this series of "laughing fits." Furthermore, contrary to ictal depression, no "ictal euphoria" was present during such laughing fits as far as could be determined. These laughing fits apparently were predominantly motor phenomena. It is interesting to note that all 4 subjects were children who are more seizure prone than adults.

The electroencephalographic abnormalities indicated a wide variety of disturbances, such as focal temporal spiking and slowing, spike-dome variant formations and diffuse slowing (patient K.R. following operation and irradiation, Fig. 1C). This corresponds with the observations by Druckman and Gibbs and Gibbs[7] in 4 patients. However, when we could record laughing fits electroencephalographically, (patients R.J. and T.J.) invariably we noted evidence of abnormal focal, temporal lobe activity. This corresponds with the observation by Daly and Mulder[2] in their first case in which

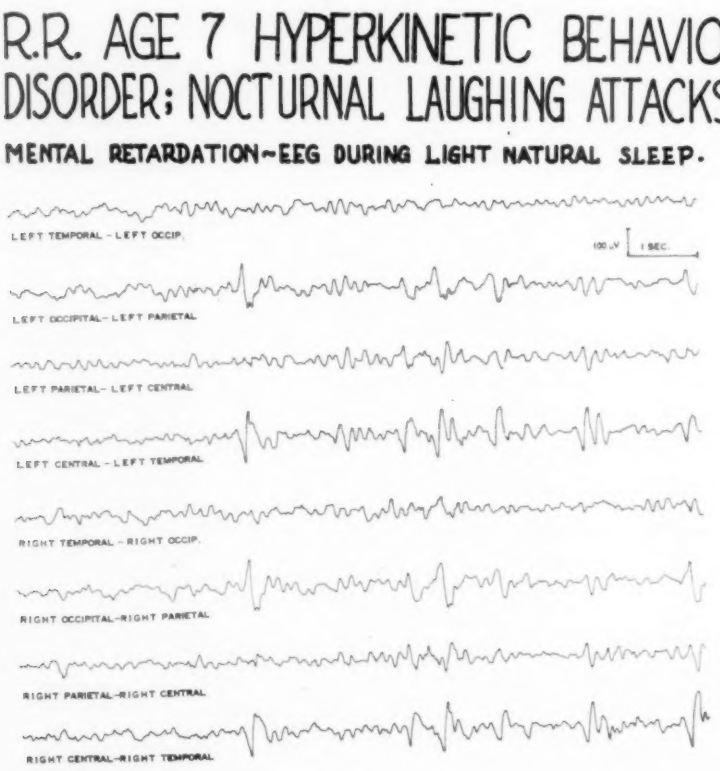
R.R. AGE 7 HYPERKINETIC BEHAVIOR DISORDER; NOCTURNAL LAUGHING ATTACKS
MENTAL RETARDATION~EEG DURING LIGHT NATURAL SLEEP.
LEFT TEMPORAL - LEFT OCCIP.
100 μV
1 SEC.
LEFT OCCIPITAL - LEFT PARIETAL
LEFT PARIETAL - LEFT CENTRAL
LEFT CENTRAL - LEFT TEMPORAL
RIGHT TEMPORAL - RIGHT OCCIP.
RIGHT OCCIPITAL - RIGHT PARIETAL
RIGHT PARIETAL - RIGHT CENTRAL
RIGHT CENTRAL - RIGHT TEMPORAL

Fig. 4.—6/17/57. Light natural sleep EEG shows slow and occasional sharp spikes in isolated fashion and in brief aggregates bilaterally synchronous over occipital-parietal and central-temporal linkages.

Chao[3] of their 11 cases. However, we did not observe hypsarrhythmic patterns such as described by Druckman and Chao[3], probably because our subjects were somewhat older children. We did *not* observe 14 and 6/sec. positive spikes as noticed by Druckman and Chao[3] in one of their cases and by there was an infiltrating tumor of the left temporo-occipital region.

Are these seizures actually derived from temporal lobe centers, or is the temporal lobe only the projection area of a larger system? The literature indicates that "laughing fits" occur, not infrequently, in lesions involving areas

around the third ventricle and diencephalon. In 1934, Foerster and Gagel[6] described a patient with papilloma of the choroid plexus having laughing fits similar to our case, K.R. These fits could be reproduced mechanically by sponging the floor of the third ventricle. Martin's[11] case with "uncontrollable laughing fits" had an aneurysm at the termination of the basilar artery which was found to extend vertically into the interpeduncular space, compressing the corpora mammillaria and part of the floor of the third ventricle. Dott[1] describes a child with an astrocytic tumor involving the corpora mammillaria and part of the third ventricle having fits of meaningless laughter. Recently Stern and Brown[13] described pathological laughter in a patient with a metastatic melanoma involving diencephalic and upper brain stem areas.

Not all of these cases mentioned in the literature had extensions of their lesions into temporal lobe structures; yet they had laughing fits. Druckman and Chao's[3] 11 children had various kinds of convulsive disorders, most of them apparently referable to disturbances of hypothalamic deep midline structures.

Stern and Brown[13] have postulated that a diencephalo-mesencephalo-integrating center responsible for emotional expression might have been stimulated with an epileptic-like discharge. In our patient, K.R., we had anatomical evidence of third ventricle-midbrain destruction due to an advancing tumor. Our patient, R.J., had evidences of mesencephalic seizures (as described by Penfield and Jasper[12]), assuming tonic "frozen" positions and drooping of the left eyelid preceding laughing fits. This patient was thought to have postencephalitic seizures.

As long as we have evidence that epileptic laughing fits may occur in disturbances of diencephalic-mesencephalic areas as well as of temporal lobe structures, we might assume that these seizures, similar to other "seizures of emotional expression," are referrable to the limbic system. MacLean[10] has pointed out that this system (great limbic lobe of Broca, including hippocampus, and its subcortical cell station, that is, amygdala, septal nuclei, hypothalmus, anterior thalamic nuclei, parts of the basal ganglia, and others) perhaps is the most important regulator for a variety of viscerosomatic and emotional reactions in mammals. The temporal lobe discharges observed in our EEG's probably originated in deeper diencephalic-mesencephalic cell stations of this system; whereas the EEG recorded only the discharge in the final receiving station, namely, the temporal lobe.

Summary. (1) Four children having unmotivated epileptic laughing fits were electroencephalographically studied. Clinical diagnoses were as follows: (1) Papilloma of the third ventricle, infiltrating into the tip of the temporal lobe. (2) Postencephalitic, mesencephalic seizures. (3) "Birth trauma" with mental retardation, akinetic-motor and temporal lobe seizures. (4) "Birth trauma" with hyperkinetic behavior disorder and nocturnal laughing fits.

(2) The epileptic nature of these laughing fits was demonstrated by the fact these laughing fits were inappropriate to any environmental factors; that they preceded or were a part of other epileptic phenomena; and that all 4 subjects had paroxysmal EEG abnormalities.

(3) Interseizure electroencephalograms showed a wide variety of abnormalities, such as focal temporal spiking and slowing, spike-dome variant formations and diffuse slowing in one patient (following neurosurgical intervention but with continuation of laughing fits). Electroencephalographic re-

cordings were obtained in 2 patients during laughing fits and both were characterized by focal, temporal lobe discharges.

(4) A review of the literature makes it apparent that laughing fits are prone to occur in disturbances around third ventricle areas and diencephalon, with projection to the temporal lobe. Our own electroencephalographic and neurological experiences indicate the possibility of limbic area activation as being responsible for epileptic laughing fits.

ACKNOWLEDGMENT: The technical help of Dr. Ilona Glaser in obtaining EEG recordings is herewith acknowledged.

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(Interlingua on page 300)

SUMMARIO IN INTERLINGUA

(See page 309 for original article)

Le Effecto Hematopoietic De Micre Doses De Ferro In Voluntarios Subjicite A Phlebotomias Repetite: Con Un Nota In Re Le Addition De Acido Ascorbic

Anemia inducite in masculos in bon stato de sanitate per repetite phlebotomias de 500 ml pote esser corrigite per le administration oral de micre doses de sulfato ferrose, 150 mg per die, in un forma a liberation continue que pote garantir que solmente un micrissime portion del sal de ferro es liberate in le stomacho e que le disturbationes gastrointestinal cognoscite ab le therapia a ferro conventional es practicamente eliminate.

Le addition de acido ascorbic non es necessari pro promover le absorption de ferro in forma a liberation continue intra le intestino tenue.

HEMATOPOIETIC EFFECT OF IRON IN SMALL DOSES ON REPEATEDLY PHLEBOTOMIZED VOLUNTEERS: WITH A NOTE ON THE ADDITION OF ASCORBIC ACID

By R. Philip Custer, M.D.

James Butcher, M.D.

Raymond Conover, M.D.

and

Walter Cervoni, M.D.

(From the Laboratories of the Presbyterian Hospital in Philadelphia, and the Department of Pathology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania)

Clinical experience with iron salts, especially ferrous sulfate, has given us the impression that the doses generally prescribed are well in excess of actual requirements of the patient. We have noted that anemia really due to deficiency of iron for whatever cause could be corrected by the administration of a ferrous salt of one sort or another in rather modest doses as gauged by current practice. For example, 300 mg. of ferrous sulfate daily was generally effective, whereas the recommended dose of this compound is 900 to 1200 mg. per day.

The opportunity to evaluate this impression more precisely arose in connection with the trial of a new orally administered iron preparation in sustained release form*. This is a capsule containing 150 mg. of exsiccated ferrous sulfate (47 mg. of elemental iron) divided into many small pellets which are selectively coated to release approximately 10% of the iron salt in the stomach and disperse the remainder throughout the small intestine, preserving its bivalent state until it is made available for absorption at the various levels.

Because ascorbic acid is credited with increasing the amount of iron absorbed by preventing ferrous iron from being oxidized to the poorly assimilated ferric form, a second type of capsule was employed, incorporating 75 mg. of ascorbic acid which was also in sustained release pellets.

The sick human is the poorest of experimental animals, presenting so many variables that a simple clinical trial of the test preparations would be inconclusive *per se*. Lower animals suitable in most respects for the experiment, such as the dog, metabolize iron in a fashion somewhat different from the human. Consequently, this initial study was made on normal men who volunteered as subjects for a controlled phlebotomy experiment.

Material and Methods. Ten healthy medical students, all males of average height and weight, whose ages ranged from 22 to 26 years, were selected for the study. Each was bled of 500 ml. at the outset of the experiment and again 1, 2, 3, and 5 weeks later, for a total blood loss of 2,500 ml. Each week before the phlebotomy, and for 3 weeks after bleeding was discontinued, they were questioned concerning symptoms related to anemia, given careful physical examinations,

*Feosol *Spansule* Capsules, supplied for investigational use by the Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

and subjected to the following laboratory studies: Hemoglobin level (photoelectric cyanmethemoglobin method), erythrocyte count (turbidometric and chamber), microhematocrit (Drummond), and serum iron and ascorbic levels*. Because of diurnal variation in serum iron, all of the studies were performed on samples obtained at or about 9 A.M. and preceded the phlebotomies on the bleeding days.

Treatment was begun after the third bleeding, when a consistent fall in hemoglobin and serum iron values signified depletion in iron reserves. Five men received one capsule daily containing 150 mg. of exsiccated ferrous sulfate in sustained release form, the other five being given similar capsules with 75 mg. of ascorbic acid incorporated in the pellets. No other medication was given, and all of the subjects remained on their normal diets, estimated to contain 10 to 15 mg. of iron daily. Dietary vitamin C was restricted by eliminating citrus fruit and tomato juices.

As our experiment paralleled to some extent those of Finch, Haskins and Finch[2] and Coleman, *et al.*[1], the rate of hematopoiesis was computed according to their assumptions, so that certain comparisons might be drawn. They proposed that:

1. Total volume of blood per person = 5700 ml.
2. Total mg. erythrocytes = hematocrit × 5700
3. Normal weekly erythrocyte regeneration = 7% × total mg. erythrocytes

From these propositions, the rate of red cell regeneration during the week following each phlebotomy may be calculated:

1. Erythrocyte replacement (A) = 7% × hematocrit before previous phlebotomy × (5700 ml. − 500 ml.)
2. Cells removed (B) = 500 × hematocrit before previous phlebotomy
3. Cells not replaced (C) = 5700 × (hematocrit before previous phlebotomy − hematocrit before next phlebotomy)
4. Mg. erythrocytes generated during week following phlebotomy = A + B − C.

Results. None of the men experienced significantly unpleasant effects of their repeated blood loss, and no alarming physical findings were observed. Several of them were members of interfraternity basketball teams and continued to play throughout the experiment. One man mentioned that he was "a bit more dyspnoeic" than usual toward the end of a game, but was not particularly concerned over it. There were no complaints of digestive disturbances. Close observation of the feces failed to disclose undissolved pellets, and there was very little darkening in the color.

The decline anticipated in hemoglobin, erythrocyte, hematocrit, and serum iron levels following the first two bleedings without supplemental iron therapy was much the same in each man, the average of the group being shown in Figs. 1 to 4. Despite the small amount of ferrous sulfate administered immediately after the third phlebotomy (150 mg. in sustained release form daily), the fall in all of these values was checked through the fourth one, and the levels rose slightly after the one-week respite. This is most clearly demonstrated in the graph of microhematocrits (Fig. 3), in that the standard deviation for the method is virtually negligible. The final bleeding at the sixth week brought about another dip in all curves, however slight, but a steady increase became evident during the final weeks of the experiment in all but serum iron levels (Fig. 4).

The decrease in serum iron was proportionately greatest of all factors measured during the period prior to introduction of the iron supplement. Thereafter, these values maintained a fairly constant level, with little or no tendency to rise. However, one would not anticipate any significant increase until the hemoglobin deficiency was compensated, and normal tissue iron stores re-established.

One of the most interesting features of the experiment was the calculated

*All laboratory studies were performed by Beryl Harrison, B.S., M.T. (ASCP). We are greatly indebted to Miss Harrison for her interest in the project, and for the exceptional precision of her work.

Hemoglobin %

RBC Million

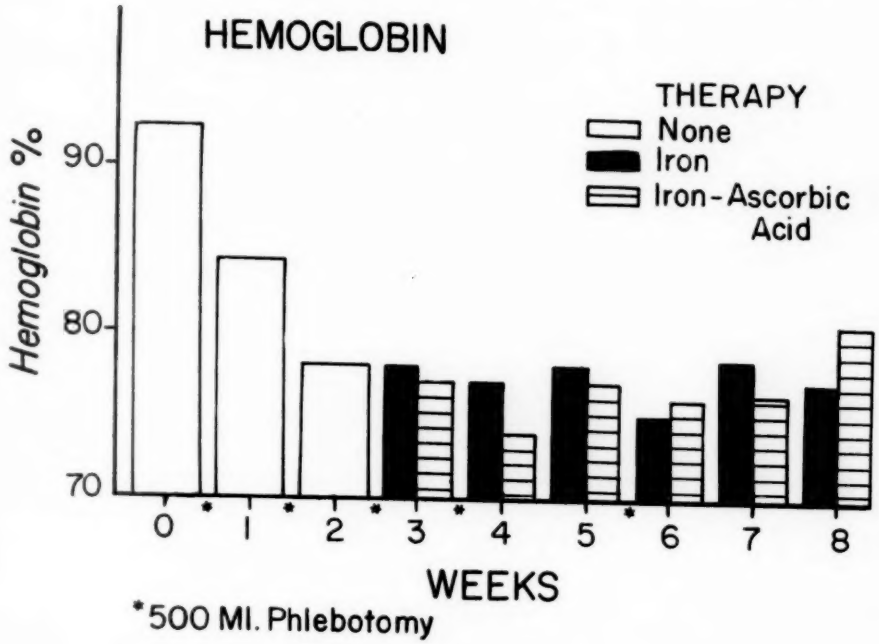
HEMOGLOBIN
THERAPY
None
Iron
Iron-Ascorbic Acid
Hemoglobin %
90
80
70
0 * 1 * 2 * 3 * 4 5 * 6 7 8
WEEKS
*500 Ml. Phlebotomy

Fig. 1

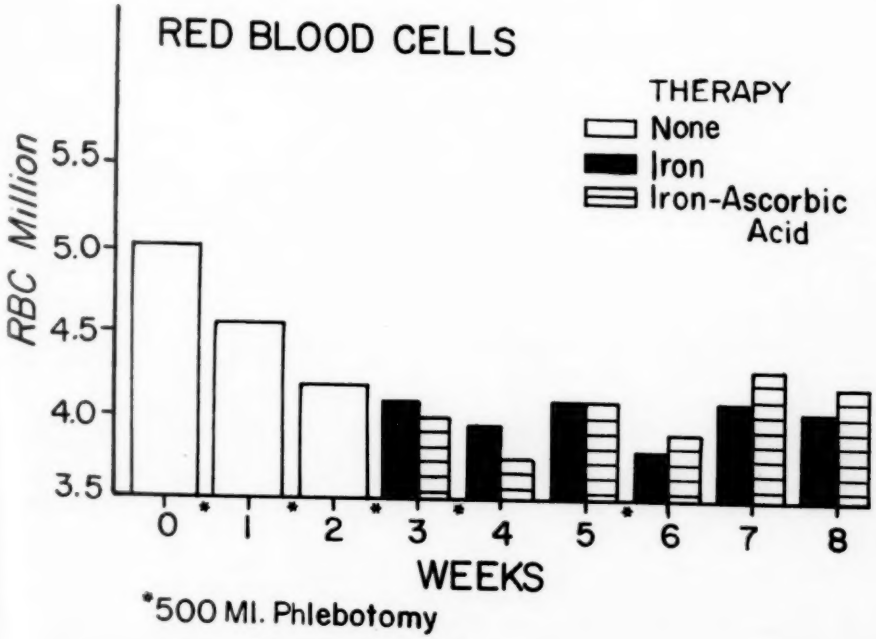
RED BLOOD CELLS
THERAPY
None
Iron
Iron-Ascorbic Acid
RBC Million
5.5
5.0
4.5
4.0
3.5
0 * 1 * 2 * 3 * 4 5 * 6 7 8
WEEKS
*500 Ml. Phlebotomy

Fig. 2

rate of hematopoiesis in connection with the rate of deficit of the red cell mass, each expressed in percentage (Fig. 5). Prior to administration of iron, both curves fell, the former only slightly, the latter very significantly. With the advent of therapy, however, the rate of hematopoiesis rose sharply and the downward trend of red cell deficit was slowed. The rate of hematopoiesis then fell while the deficiency was being made up. A slight increase was again noted after the last phlebotomy, with a normal value recorded a week later; the minor deviation at the eighth week is regarded as remaining within the norm.

Figures 1, 2, 3, 4, and 6 differentiate the 5 men who were given ferrous sulfate alone and the 5 whose iron therapy was supplemented with ascorbic acid. The two groups had been carefully matched at the outset of the experiment as to physical habitus as well as blood levels. As one would expect, the ascorbic acid was well absorbed and served to raise the serum level to about 30% over that of the men who were not given the supplement (Fig. 6). However, there was no significant difference between the two groups with respect to absorption and utilization of iron.

Discussion. The major concern in the experiment was the effectiveness of much smaller than usual amounts of a ferrous salt in making up a deficit in hemoglobin created by repeated bleeding of normal young men. A secondary concern lay in the degree of absorption of the iron when it was administered in sustained release form, with most of it being liberated beyond the stomach for the purpose of avoiding gastric irritation. A minor concern was the influence of ascorbic acid on absorption of iron from the intestinal tract, where conversion of a

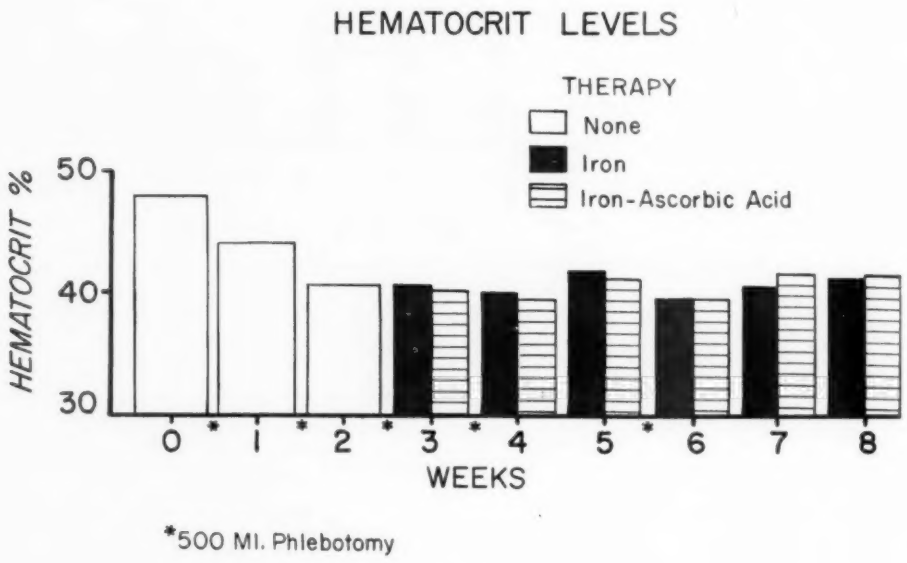

Fig. 3

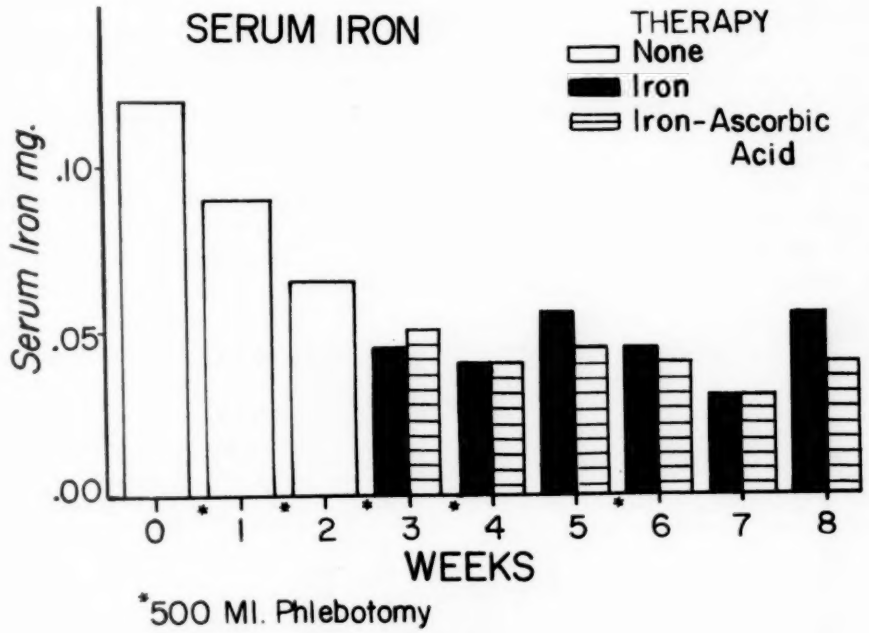
SERUM IRON
THERAPY
None
Iron
Iron-Ascorbic Acid
Serum Iron mg.
.10
.05
.00
0 1 2 3 4 5 6 7 8
WEEKS
*500 Ml. Phlebotomy

Fig. 4

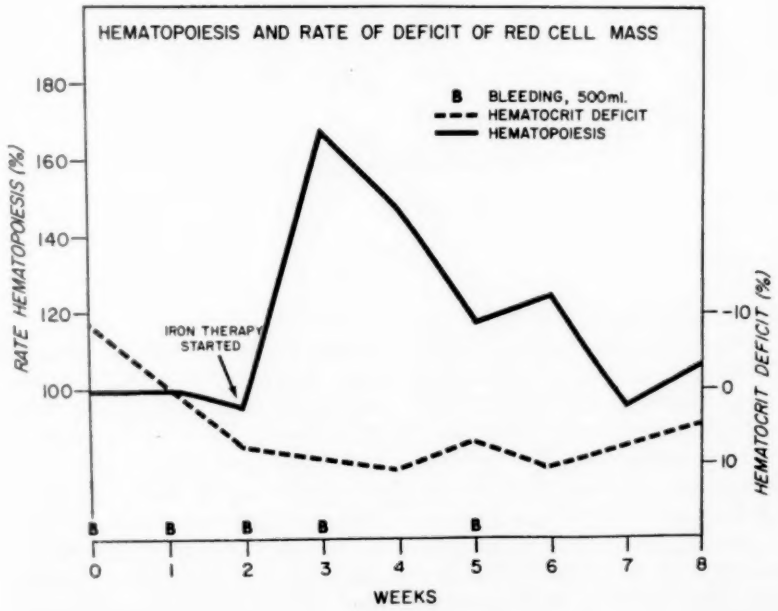
HEMATOPOIESIS AND RATE OF DEFICIT OF RED CELL MASS
B BLEEDING, 500ml.
HEMATOCRIT DEFICIT
HEMATOPOIESIS
RATE HEMATOPOIESIS (%)
180
160
140
120
100
IRON THERAPY STARTED
-10
0
10
HEMATOCRIT DEFICIT (%)
B B B B B
0 1 2 3 4 5 6 7 8
WEEKS

Fig. 5

ferrous to a ferric salt might be expected to take place rapidly and thereby restrict absorption.

It would have been ideal to have conducted parallel experiments with a second group receiving the same dose of ferrous sulfate in powdered form, and a third to whom the much larger standard therapeutic dose was administered. It was difficult enough, however, to obtain 10 volunteers for the key experiment, and we, as investigators, were constantly troubled over the welfare of the subjects who were being bled weekly, sufficiently so that we postponed the scheduled fourth phlebotomy for a week, and thereby lost pace with a possibly comparable experiment conducted by others (Finch, Haskins and Finch[2]). The experience of one of us with the incidence of unsuspected coronary insufficiency and sudden death among young soldiers during World War II was responsible for our timidity in expanding the experiment into the 2 desirable control phases.

Next best was a comparison of our results with those of Finch, Haskins and Finch[2]. Eight of their subjects (excluding their cases of frank hemochromatosis) were subjected to 7 weekly phlebotomies of 500 ml. each and received no iron supplement. The ninth was given 600 mg. of ferrous sulfate by mouth, and the tenth 1,200 mg., beginning with the first bleeding. Our group did not receive treatment (150 mg. per day) until 3 phlebotomies had been performed, and iron stores had been significantly depleted. Perhaps compensation may be furnished by our men having missed their scheduled fourth bleeding, and having been bled only once thereafter. Nonetheless, it is shown in Fig. 7 that the fall in

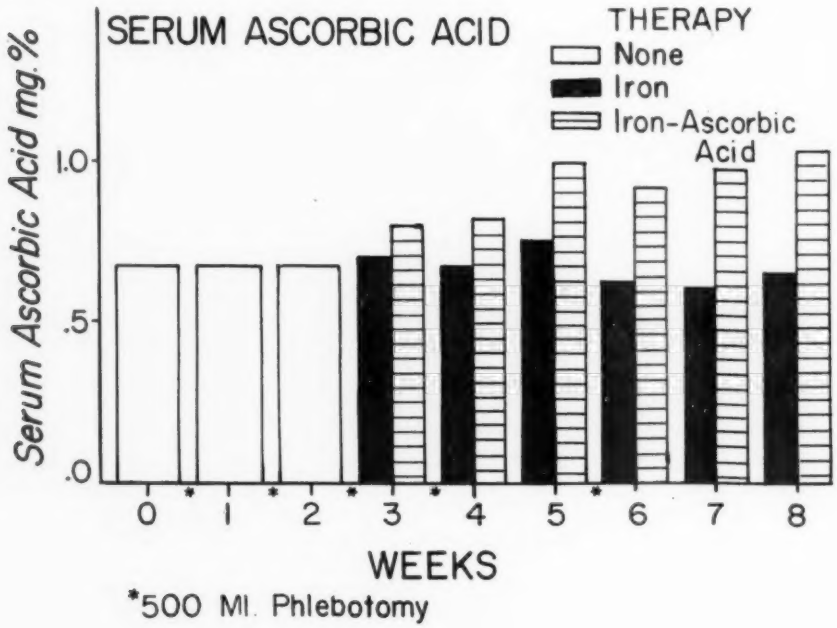

Fig. 6

hematocrit over the first 4 weeks was essentially the same in all subjects (it is unfortunate that Finch, Haskins and Finch did not record hemoglobin levels). Beyond this point, Finch's untreated men continued their decrease in hematocrit levels, while the treated men showed a decided upswing. The rise was not so pronounced in our group, but the differential was in no sense comparable. Had our group been

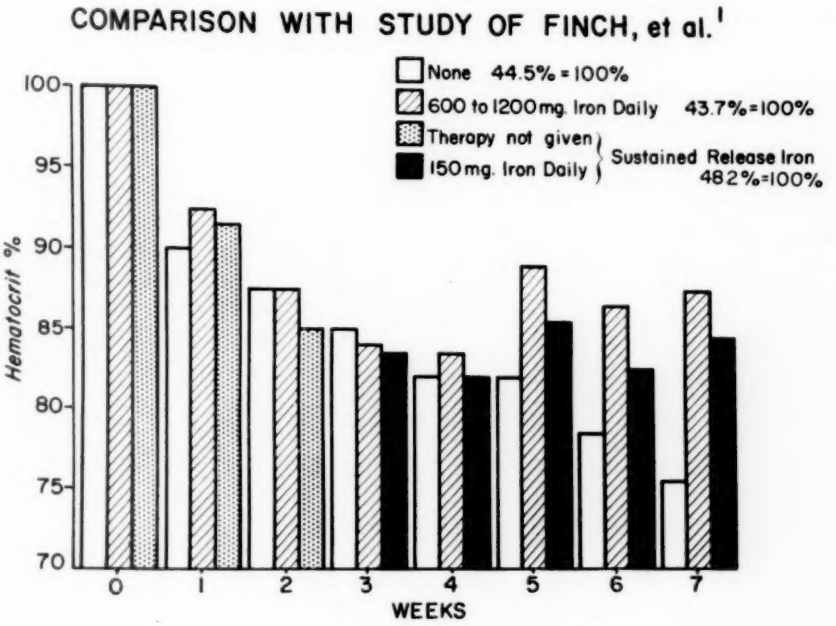

Fig. 7

given the smaller dose of ferrous sulfate from the very outset, we doubt whether there would have been any significant difference between their blood levels and those of the two who received 4 and 8 times the amount, respectively.

The matter of concomitant administration of ascorbic acid is of some practical interest. Most of the commercial preparations containing inorganic iron have ascorbic acid as one of their many additives, based on the assumption that a reducing agent will hold the iron in ferrous form for maximal absorption, which is unquestionably true. However, the amount of ascorbic acid in such compounds varies from 20 to 150 mg., mostly 50 mg., and always well below the quantity of the iron salt. The maximum quantity of ascorbic acid practicable for incorporation in our sustained release capsule was 75 mg., which we regarded as generous for comparison with commercial products. Nonetheless, our results disclosed no significant difference in hemoglobin regeneration induced by ascorbic acid in the quantity administered. Thus, either the reducing agent was present in insufficient amount or the ferrous sulfate liberated from the pellets in the intestine was absorbed before much conversion to the ferric salt had taken place. The former may

well be a factor, as judged by the experiments of Moore and Dubach[4] who studied several series of persons given food in which radioiron was incorporated, undoubtedly in *organic* compound. Among their observations was the fact that the absorption of Fe^{59} from food could be enhanced by ascorbic acid, foods containing ascorbic acid, and to a lesser extent by other reducing agents such as cysteine. It required rather large amounts of these substances, however, to bring about significantly greater assimilation of the tagged iron, 1 gm. of ascorbic acid added to the test meal, for example.

With respect to the effect of reducing agents on absorption of *inorganic* iron salts, Groen's[3] experiments on isolated loops of jejunum in the rat indicated that much the same conditions obtain. There was no detectable uptake of 500 mcg. of ferrous sulfate introduced into such a loop unless a considerable quantity of reducing substance was added, ascorbic acid being the best. Even so, it required 10 mg. of the latter to bring about a notable difference, and 50 to 100 mg. for the upswing to be uniformly pronounced. It would seem, then, that the token component of ascorbic acid in the proprietary "hematinic capsules" serves mainly to embellish the label and increase the cost to the patient.

While the ideal experiment remains to be carried out, it seems rather obvious that our concerns over the adequacy of small doses of ferrous sulfate in correcting iron deficiency states produced by chronic bleeding, the adequacy of the small intestine in absorbing ferrous sulfate administered in sustained release form, and the unimportance of ascorbic acid as an adjunct for absorption of iron given in this fashion have been satisfactorily allayed.

Conclusions. Anemia induced in healthy males by repeated phlebotomies of 500 ml. can be corrected by the oral administration of small doses of ferrous sulfate (150 mg. daily) in sustained release form, whereby very little of the iron salt is liberated in the stomach, and gastrointestinal disturbances from conventional iron therapy can virtually be eliminated.

The addition of ascorbic acid is not necessary to promote the absorption of iron in sustained release form from the small intestine.

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(Interlingua on page 308)

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ROGER W. REED, M.A., M.D., C.M.
PROFESSOR OF BACTERIOLOGY AND IMMUNOLOGY, McGILL UNIVERSITY

AND

GARDNER C. McMILLAN, M.D., C.M., M.Sc., PH.D.
STRATHCONA PROFESSOR OF PATHOLOGY, McGILL UNIVERSITY
MONTREAL, CANADA

BACTERIAL NEUROTOXINS

BY J. W. STEVENSON, M.D., C.M.
DEPARTMENT OF BACTERIOLOGY AND IMMUNOLOGY, McGILL UNIVERSITY
MONTREAL, CANADA

IF one defines a bacterial neurotoxin, in the strictest sense of the term, as a substance which acts specifically on nerve tissue in such a way as to account for the major symptoms of the disease process, then it is undoubtedly true that the elaboration of neurotoxins concerned in human disease may be attributed to only two bacterial species, *Clostridium botulinum* and *Clostridium tetani*, the causal agents of botulism and tetanus respectively. The most potent nerve poisons known to man are produced by these two species of the anaerobic spore-forming bacteria. In virtue of their extraordinary potency and the dramatic symptoms that they induce, botulinum and tetanal toxins have received, over the years, much attention from investigators in various fields such as bacteriology, biochemistry and neurophysiology.

There are a few infectious diseases of bacterial origin in which neurotoxic symptoms may appear infrequently, diseases in which such symptoms are regarded more as complications than as integral parts of the clinical picture. It has not been established with certainty whether involvement of the nervous system in such instances is due to specific neurotoxic substances or whether the neurological symptoms are due to the same toxins as those which account for the classical symptoms. The best example of an infectious disease in which well defined neurological symptoms of toxic origin may appear as a late complication is diphtheria.

There is, on the other hand, at least one instance of a bacterium which produces a toxin capable of inducing a well defined paralytic syndrome in laboratory animals but which appears to produce no neurological symptoms

of significance in the naturally occurring human disease, or if so, only in the exceedingly rare instance. This is *Shigella dysenteriae*, the causal agent of a severe form of bacillary dysentery.

Botulinum Toxin. Botulism is a form of food poisoning which follows the ingestion of preserved foodstuffs in which *Cl. botulinum* has grown and elaborated toxin. The disease is a pure intoxication, unaccompanied by infection, since the organism, a soil saprophyte, has no capacity to establish itself in living tissues under ordinary conditions. Symptoms have their onset within 12 to 72 hours after ingestion of the spoiled food and tend to take the form, initially, of visual disturbances as diplopia, blepharoptosis, mydriasis and loss of reflex to light. Pharyngeal and laryngeal paralysis also tend to occur early and eventually the paralysis extends to involve the skeletal musculature. Death, when it occurs, is due to respiratory paralysis or cardiovascular collapse. The mortality rate in North America has been about 65%; fortunately the disease is not a common one. In those who survive, some months are ordinarily required for complete return to muscle function.

Five distinct types of the single species *Cl. botulinum* designated A, B, C, D and E, are recognized on the basis of serological specificity of the toxins that they produce. There would appear to be two closely related strains of the type C organism, Cα and Cβ. The Cα antitoxin neutralizes both the Cα and Cβ toxins whereas the Cβ antitoxin neutralizes only the homologous Cβ toxin. Despite their antigenic dissimilarity all five toxins produce identical symptoms and there is no reason to believe that they differ in the mechanism by which they produce paralysis. They do, however, differ quite markedly in their potency for different animal species. Botulism in man has been due exclusively to the A, B, and E toxins. Types C and D have been associated with the disease only in the lower animals, the Cα toxin accounting for large outbreaks of botulism in wild ducks and the Cβ and D toxins causing naturally occurring botulism in cattle, horses and sheep. The Rhesus monkey is resistant to the C and D toxins when they are administered *per os*[59], and it is possible that man is equally insusceptible, since these types have not been implicated in human botulism.

PROPERTIES OF BOTULINUM TOXIN. Of the five toxin types the A toxin has been the one most intensively studied. Whole culture autolysates of very high potency may be obtained by growing the organisms in media containing casein or tryptic digests of casein, glucose and corn-steep liquor[75,114,115]. In such media the yield of toxin ranges from 1 to 2 $\times$ 10^6 mouse intraperitoneal LD 50's per ml. of culture autolysate. Barron and Reed[12] have produced type A cultures containing 40 to 50 million lethal mouse doses per ml. by growing the organisms in cellophane sacs suspended in a peticase, glucose, corn-steep medium. Botulinum toxin is not one of those products which are actively secreted by growing cells. It would appear rather to be an integral part of the protoplasm which is only liberated into the culture fluid when the cells undergo autolysis[22,23,114]. The toxin was isolated in pure crystalline form by two groups working independently and employing different methods (Abrams, Kegeles and Hottle[7], Lamanna, Eklund and McElroy[70]). It was the first bacterial toxin to be obtained in crystalline form. Abrams *et al.*[7] precipitated the toxin from the culture autolysate at pH 3.5. Fractional precipitation of a solution of the toxin concentrate with ethanol and sodium sulphate yielded the crystalline prod-

uct. Lamanna's procedure[70] involved shaking a neutral solution of acid precipitated material with chloroform to remove nucleic acids which form a gel and repeated fractionation of the aqueous phase with acid and ammonium sulphate. Duff *et al.*[43] have, within the past year, described a simplified procedure for purification of the type A toxin involving its extraction from acid precipitates with 0.075 M calcium chloride followed by acid and ethanol precipitations.

The type A toxin is a heat coagulable protein with the solubility properties of a globulin. The intraperitonal LD 50 for the 20-gm. white mouse is approximately 0.00003 gamma (32 billion mouse LD 50's per gm. of pure toxin and 220 to 240 $\times$ 10^6 LD 50's per mg. of nitrogen[70]). If one assumes man to have the same degree of susceptibility, on a unit weight basis, as the mouse, and there is every reason to believe that he has, then the lethal dose for an adult of average weight would be approximately 0.12 gamma by injection. This toxin is the most poisonous substance known and despite the fact that the lethal dose *per os* is somewhat higher than by parenteral injection, it is not surprising that individuals have contracted fatal botulism through simply tasting foods suspected of spoilage. The guinea-pig is some two times more susceptible to the toxin on a unit weight basis than is the mouse[114]. The estimated isoelectric point of the toxin based on electrophoresis data is pH 5.6[7]; the molecule contains 16.29% nitrogen, 0.052 to 0.059% phosphorus and 0.437% sulphur[27]. The molecular weight, calculated on the basis of physical data has been placed at 900,000 by Putnam, Lamanna and Sharp[107], and at 1,130,000 by Kegeles[66]. Assuming a molecular weight of 900,000 it may be calculated that only 2 $\times$ 10^7 molecules are necessary to kill a mouse. Nineteen amino acids have been identified in the crystalline toxin and they account for all of the nitrogen[27]. Buehler, Schantz and Lamanna[27] suggest the following empirical formula in terms of amino acid residues: Gly_{166}, Ala_{394}, Val_{406}, Leu_{708}, $Ileu_{820}$, Pro_{203}, Phe_{64}, $CySH_{20}$, $(Cy\ S\text{–})_{40}$, Met_{64}, Try_{82}, Arg_{239}, His_{60}, Lys_{477}, $(Asp\text{–}NH_2)_{1370}$, Glu_{953}, Ser_{374}, Thr_{642}, Try_{672}. The analytical data provide no explanation for the extreme toxicity of the molecule. The amino acids are naturally occurring forms, biologically active and connected through peptide bonds. The percentages of aspartic acid, tyrosine and threonine are higher than are generally encountered in nontoxic proteins of known composition[27]. The significance of this in terms of toxicity is not clear. Biological activity of the protein molecule is undoubtedly accounted for by configuration rather than elemental and amino acid configuration. Denaturation of the molecule, accompanied by a loss of solubility leads to irreversible detoxification[70]. Since the initial crystallization of type A botulinal toxin, some doubt has arisen about the purity of the preparations. Lamanna[68] first noted that the purified toxin had the capacity to agglutinate the red cells of a number of animal species. It has been since found[72] that a type B botulinal antitoxin is capable of neutralizing the hemagglutinating activity of the type A toxin, whereas it has no effect upon its toxicity. Agar diffusion techniques reveal two bands when rabbit serum prepared against the crystalline type A toxin interacts with the crystalline homologous toxin. Further, by absorption on red cells the hemagglutinating activity of the crystalline product may be separated from the toxin. Thus, although the toxin behaves as a homogeneous substance in electrophoresis and ultracentrifugation studies it would

appear to contain two components. It is possible, perhaps, that the components responsible for hemagglutinating activity and toxicity may form a relatively stable complex under some circumstances. This might account for the very high molecular weight of the toxin. It has been reported[121] that crystalline botulinum toxin dissociates at an alkaline pH to much smaller molecules with no loss in potency of the preparation.

Lamanna and Glassman[71] reported the isolation of *Cl. botulinum* type B toxin in pure form in 1947, and noted that the methods available at the time for the purification of the type A toxin were not applicable to the isolation of the B type. The purified toxin appeared to be a simple protein with an estimated molecular weight of 60,000. The protein was quite soluble in water on the acid side of its isoelectric range, pH 4.5 and lower, but only slightly soluble on the alkaline side. Its toxicity for the mouse was 110 to 200 $\times$ 10^6 mouse intraperitoneal LD 50's per mg. of N. The guinea-pig is much more sensitive to the type B toxin than is the mouse on a unit weight basis.

Some confusion exists concerning the molecular weight and solubility properties of the type B toxin. Wagman and Bateman[122] have reported the molecular weight to be in the range of 500,000, a figure which approaches that of the A toxin. Duff *et al.*[42] have recently reported that their method of purification of the A toxin[43] is applicable to the B type and that A and B toxins prepared by the same procedure differ little except in serological specificity. Their potencies for the mouse are almost identical. Their solubility properties do not differ and the similarity of the sedimentation constants of the two toxins suggest that they may not differ greatly in molecular weight. It is suggested that the chemical differences noted by Lamanna and Glassman might have resulted in part, at least, from the fractionation methods involved in isolation. Whole culture autolysates of *Cl. botulinum*, type B possess, like the A toxin, hemagglutinating activity. It would be of interest to know if the low molecular weight type B preparation of Lamanna and Glassman had been freed of the hemagglutinating component and if the larger molecules prepared by others had retained this component. The type B toxin does differ, however, from the A toxin in that efforts to crystallize it have failed thus far.

Within the past few years the other type toxins C, D and E have been obtained in a purified and highly active form[31,58,124].

THE PHARMACODYNAMICS OF BOTULINUM TOXIN. Upon ingestion, botulinum toxin is absorbed, presumably from the stomach and small intestine, in a fully active state. Its potency upon ingestion may be accounted for by the fact that it is most stable at pH values of 3.5 and lower, and that in the crude form, as it exists in whole culture autolysates and spoiled foodstuffs, it is resistant to the action of pepsin and trypsin[110]. Indeed the type E toxin is markedly enhanced in potency by the action of trypsin[38,44]. It is true that the type A toxin in crystalline form although resistant to trypsin is inactivated by pepsin and chymotrypsin and it is inactive when administered to experimental animals *per os*[33]; it is possible that nonspecific substances in crude preparations may protect the molecule or perhaps facilitate its absorption into the blood stream.

Botulinum toxin is carried to nerve tissue by way of the blood; it exerts its effect specifically on nerve and affects, insofar as can be ascertained, no other tissue of the body. Symptoms referable to the central nervous system

are not seen in botulism. The lack of central involvement may be explained, possibly, by the large size of the toxin molecule which might fail to traverse the blood brain barrier.

Earlier workers[35,36,37,49,50,110] firmly established the concept that botulinum toxin exerted its effect peripherally by bringing about a block in the transmission of nerve impulses in the region of the myoneural junctions of somatic motor nerves and the parasympathetics, and actually mapped out, on the basis of the distribution of paralysis, those nerve fibers which we now recognize as cholinergic nerves. It was shown that the muscle response to direct stimulation was unaffected by the toxin and that conduction of the nerve impulse within nerve trunks, bathed in high concentrations of the toxin, was unimpaired[14]. By a process of elimination it was reasoned that the toxin acted at the myoneural junction. Guyton and MacDonald[60], Ambache[8], Burgen, Dickens and Zatman[29], Brooks[25,26] and others, have, in more recent years confirmed and extended many of the earlier observations. Most of the experimental work has been done with the type A toxin. Guyton and MacDonald employed a method of study of the effect of the toxin *in vivo* involving the production of a local paralysis in the gastrocnemius muscle of the intact living animal; Ambache has studied the local effects induced by the intraocular injection of the toxin in rabbits and Burgen *et al.* have employed in their investigations the isolated rat phrenic nerve–diaphragm preparation of Bülbring[28]. The experiments substantiate earlier claims that the toxin exerts no effect upon conduction in the nerve trunk proper nor has it any effect upon the muscle fibers as such. The specificity of the toxin for cholinergic fibers is well brought out in experiments involving intraocular inoculation where in one and the same organ adrenergic and sensory systems are unimpaired although they are exposed to a concentration of toxin which is adequate to paralyze cholinergic nerves[8].

The mechanism by which botulinum toxin blocks the transmission of nerve impulses would appear to be entirely different from the mode of action of curare. Curare renders motor end plates insensitive to the acetylcholine released from the nerve endings. This is not the case in botulism where completely paralyzed muscles remain normally responsive to the injection of acetylcholine[8,29,60]. Cholinesterase inhibitors, such as eserine and prostigmine, have a potent decurarizing action but these drugs do not, in any dose, significantly decrease the paralysis brought about by botulinum toxin[29,48,60]. Similarly such drugs as tetraethylpyrophosphate, adrenaline and KCl which are said to exert a marked anticurare action[108,126] have no appreciable effect upon the rat nerve-diaphragm preparation poisoned with the toxin[29]. It has been further demonstrated, in nerve-diaphragm preparations partially paralyzed by the toxin, that the normal type of tetanic response and normal summation curves may be obtained, a situation quite different from that seen when such preparations are partially paralyzed with curare.

Guyton and MacDonald[60] assumed that the poisoning took place at some point proximal to the site at which acetylcholine is released and postulated that the paralysis was the result of the failure of production of acetylcholine. That this is so has been substantiated by Burgen, Dickens and Zatman[29]. In rat diaphragm preparations almost completely paralyzed by the toxin, the output of acetylcholine, on motor nerve stimulation, is very markedly reduced. It appears that the poisoning follows the all or none principle, in that cholinesterase inhibitors fail to

bring about any reversal of the paralysis. It is suggested that in a partially paralyzed muscle there are some motor units which are still unaffected and behave normally in all ways and blocked motor units in which transmission cannot be restored by conditioning stimuli or other means.

In a comparison of the pharmacodynamics of A and B toxins[29], it has been shown that the rat nerve-diaphragm is relatively insensitive to the B toxin as contrasted to the A type. This correlates closely with the natural relative resistance of the whole rat to the B toxin. The guinea-pig is, on the other hand, highly susceptible to both the A and B toxins and this is reflected in experiments with the isolated guinea-pig nerve-diaphragm where the type B toxin exerts an effect as potent as that obtained with the type A toxin. It is suggested that the differing sensitivity of mammalian species to botulinum toxin of a given type is related to the sensitivity of their nerve terminals rather than to differing modes of distribution or disposal of the toxin[26,29].

There are a number of possible ways in which botulinum toxin might act at the nerve endings to bring about a diminished secretion of acetylcholine: (1) The enzymatic synthesis of acetylcholine at the nerve endings might be inhibited by the toxin; (2) acetylcholine might be destroyed as rapidly as it is formed, due to enhanced cholinesterase activity; (3) the release of acetylcholine might be prevented, perhaps by a permeability change in nerve endings; (4) although it is clearly established that the toxin exerts no effect on conduction in the nerve trunk proper, it is possible that it might block the transmision of the nerve impulse through the terminal unmyelinated fibrils, in which case the failure of production of acetylcholine would be secondary to failure of the nerve impulse to reach the "acetylcholine release" region. These various hypotheses have been investigated.

Whatever the process of botulinum intoxication, it is unlikely to be a purely physical one. In naturally occurring human botulism, despite the fact that all of the symptoms are due to a preformed toxin which demands only the process of absorption and transportation in the blood stream to reach nerve tissue, an incubation period which may range from 12 to 72 hours is seen before the onset of symptoms. When the toxin is administered to animals in doses of 1 to 2 M.L.D's., a latent period of 17 to 20 hours ensues before the onset of any signs of paralysis. Similarly a characteristic lag period is seen in isolated nerve muscle preparations bathed in the toxin[29] which cannot be explained on the basis of slow diffusion of the large molecule, since replacing the bath fluid during the latent period, a procedure which reverses the diffusion gradient into muscle, does not alter the subsequent development of paralysis. In the same light it has been noted that once the toxin has been allowed sufficient contact with nerve for fixation in isolated nerve muscle preparations, the addition of antitoxin in high doses fails to forestall the subsequent development of paralysis. There is evidence that the toxin is fixed to its "target-site" early in the latent period and produces some gradual change which ultimately leads to paralysis. The latent period is short and the progress of the paralysis most rapid at temperatures of 30 to 37° C.; at lower temperatures the latent period and progress of paralysis are very much prolonged[29]. This effect is apparent in nerve muscle preparations of both the warm blooded animals and the cold blooded animals, such as the frog. This high temperature coefficient is characteristic of a chemical reaction rather than a purely physical one.

Torda and Wolff[118] reported that the

type A and B toxins strongly inhibited the *in vitro* synthesis of acetylcholine by frog and mouse brain homogenates, and noted that brain tissue from poisoned animals synthesized some 60% less acetylcholine than did brain tissue from healthy controls. Others have failed to confirm these findings[29]. Burgen *et al.*[29] have been unable to detect any inhibitory effect of the toxin on choline acetylase activity in mouse brain homogenates or in acetone-dried powders of rat brain. The coenzyme for choline acetylase is the same as that involved in the liver enzyme system responsible for the acetylation of aromatic amines, that is, coenzyme A. Botulinum toxin has no inhibitory effect upon this system as it is involved in the acetylation of sulphanilamide[29], and it may be concluded that it does not affect coenzyme A as it functions in the acetylation of choline. That the toxin does not affect adenosinetriphosphate is obvious in that ATP must be included as a source of energy in the choline acetylating system where acetone dried powders of nerve tissue are employed as a source of choline acetylase. Stevenson, Fairbairn and Campbell[112] failed to demonstrate any effect of the toxin on adenosinetriphosphatase (ATP-ase) activity. Botulinum toxin would appear not to modify in any way the over-all respiratory activity of nerve tissue *in vitro*, nor does the Qo_2 of brain slices from poisoned animals differ from normal values[29]. The microbial synthesis of acetylcholine by a bacterium *Lactobacillus plantarum* involves a mechanism of acetylation of choline identical to that of mammalian cells[111,113]. Stevenson and Girvin[113] have shown that botulinum toxin in high concentrations does not inhibit (1) the synthesis, the secretion or the storage of acetylcholine by actively proliferating lactobacilli in culture, (2) the synthesis and secretion of acetycholine by nonproliferating suspensions of *L. plantarum* incubated in a chemically defined substrate and (3) the toxin exerts no effect upon the activity of cell-free bacterial choline acetylase nor upon other essential components of the acetylating system as coenzyme A and adenosinetriphosphate. Pappenheimer[91] has suggested that the toxin might act not by direct inhibition of components of the choline acetylating system but rather by interfering with the synthesis of some component of the system. This would explain the long lag period in botulism. However it should be noted that in an investigation of the bacterial acetylation of choline[113] that cultures of *L. plantarum* were initiated from a small inoculum, the cells reproduced themselves normally in the presence of high concentrations of toxin and the descendents of the seed cells, many generations removed from the original inoculum, synthesized acetylcholine in normal amounts.

As to the possibility of enhanced cholinesterase activity as the basis of the diminished supply of acetylcholine at nerve endings it is reported that botulinum toxin in high concentration has no effect on the activity of the "true" or the "pseudo" cholinesterases of guinea-pig serum[29]. A rapid disappearance of acetylcholine due to an enhanced cholinesterase activity may also be excluded as an explanation of the mode of action of the toxin, since the output of acetylcholine in *in vitro* experiments is measured in the presence of eserine, a cholinesterase inhibitor.

Any effect of the toxin on permeability of the "acetylcholine release" mechanism with resultant failure of the release or diffusion of acetylcholine seems unlikely, in that a permeability change in the nerve endings would not be likely to follow the all or none

principle which applies to the effect of botulinum toxin. Moreover, experiments with bacterial cells[113] indicate that the toxin has no effect upon the secretion of acetylcholine through the bacterial cell membrane. The amount actively secreted by cells bathed in high concentrations of toxin did not differ from the amount secreted by normal control cultures and the concentration of acetylcholine held or stored within the cells was the same in the presence or absence of toxin. It may be argued, of course, that bacterial cell membranes and the membranes of mammalian nerve endings may differ radically in their properties in this respect. Burgen *et al.*[29] concluded, by a process of elimination based on their observations and the experiments of others, that the toxin exerted its effect by interacting with some component of the terminal unmyelinated nerve fibrils entering the end plate region in such a way as to block transmission of the nerve impulse. The failure of production of acetylcholine would then be secondary to the failure of the stimulus to reach the "acetylcholine release" region; this is in accord with the all or none principle of botulinum poisoning. This theory is supported by Brooks[25,26], who studied action potentials in the end plate zone of single motor units in poisoned muscle preparations, and demonstrated that botulinum toxin renders terminal motor nerve filaments, just proximal to the end plates, inexcitable to impulses originating in the nerve trunk proper. Brooks points out that the acetylcholine release mechanism *per se* is unimpaired in that, although it is not activated by way of the poisoned terminal nerve filaments, it is still responsive to electric current impulses applied directly through the surrounding bath medium. It is assumed that the toxin acts either by rendering the unmyelinated filaments impermeable to ions or by hyperpolarizing their cellular membranes, since action potentials impinging repeatedly on the block produced by toxin do restore conduction in the fibrils for short periods of time. Stover *et al.*[116] in a study of summation curves in isolated frog nerve-muscle preparations noted that spaced repeated stimuli applied by way of the nerve trunk within 4 to 18 msec. resulted in a muscle action potential. Their interpretation is that the first stimulus releases only a threshold quantity of acetylcholine which when added to that released by the second stimulus is sufficient to induce muscle contraction. It is argued that the paralytic effect of the toxin is due, not to impairment of conduction but rather to poisoning of the acetylcholine release mechanism. It would appear that differences in opinion as to the exact site of action of the toxin are to some extent a reflection of different interpretations of the available experimental data.

Botulinum toxin does not appear to act as a destructive poison, that is, in the sense of producing specific histological changes in the end plate region, although some swelling of end plates has been noted[60]. The period required for complete recovery of a totally paralyzed muscle in experimental animals is one year, some ten times the period required for recovery following crushing of the nerve. Guyton and MacDonald[60] suggest, on the basis of this observation, that the toxin exerts its effect, whatever it may be, at some point which cannot be repaired or reconditioned as quickly as can the nerve fibrils.

Immunization experiments contribute little to our knowledge of the mode of action of botulinum toxin except, perhaps, to point to the irreversible nature of the poisoning. The dia-

phragms of actively immunized rats show *in vitro* a 100-fold increase in resistance to homologous toxin which cannot be explained as due to occluded serum, since an amount of serum from the same animals equal to about three times the volume of the diaphragm fails to give the same protection[29]. Resistance would appear to be a tissue immunity which renders the nerve terminals refractory to the action of the toxin. Passive immunization of isolated nerve-diaphragm preparations follows the same rules as apply in passive immunization of the living animal. The addition of antitoxin prior to the union of homologous toxin and nerve tissue prevents the development of paralysis, whereas treatment with antitoxin late in the lag period or subsequent to the appearance of paralysis fails to prevent or to bring about any reversal in the progress of the paralysis.

Tetanus Toxin. Tetanus is akin to botulism in that all of the symptoms of the disease are due to the specific action of a potent toxin on nerve tissue. It differs, however, in its pathogenesis, from botulism in that there is infection, the toxin being elaborated by the growth of the organisms in the tissues. Tetanus is a disease which may occur in man and the lower warm-blooded animals when the spores of the anaerobic spore-forming bacterium, *Cl. tetani*, gain entry into wounded or otherwise injured tissues. The spores will only germinate and the vegetative forms multiply in dead fragments of tissue or foreign materials in the wound where conditions of anaerobiasis prevail, as a result of which we have in tetanus a strictly localized infection which may, at times, be insignificant in extent even in a fatal case. The manner in which the neurotoxin, which is elaborated locally in the wound, makes its way to the central nervous system where it exerts its major effect, has been a subject of much controversy over the years. The clinical features of tetanus are too well known to deserve attention in detail here. The incubation period may range in cases where no prophylaxis has been attempted, from 2 to 21 days. Not infrequently the first symptoms take the form of local tetanus with spasm and rigidity of the muscles in the neighborhood of the wound. Generalized tetanus develops insidiously with gradually increasing stiffness and tonic spasms of the skeletal muscles. Trismus or tonic spasm of the masseters is often an early and characteristic sign; the muscles of the trunk and limbs are gradually involved. Any slight stimulus, tactile, auditory or visual may initiate a reflex paroxysm of violent muscular contractions. The clinical picture differs from strychnine poisoning in that there is in tetanus a sustained muscular rigidity between the reflex paroxysmal seizures. The mortality rate bears a definite relationship to the incubation period. It may be as high as 80% when the incubation period is very short, or as low as 17% when the incubation period is much prolonged.

PROPERTIES OF TETANUS NEUROTOXIN. *Cl. tetani* produces at least two antigenically distinct toxins, a hemolysin (tetanolysin) and a highly potent neurotoxin variously referred to as spasmin, tetanospasmin, tetanus neurotoxin or more simply as tetanus toxin, since tetanolysin may be disregarded in that it plays no part in the development of the toxemia. Although a number of types of *Cl. tetani* are recognized on the basis of flagellar antigens[76], all strains, unlike *Cl. botulinum*, produce the same type of neurotoxin which can be neutralized by a single antitoxin. Tetanus toxin may be prepared in a variety of media, such as media composed largely of hog stomach autolysate and beef heart infusion[85,117], or

a tryptic digest of casein supplemented with cystine, tyrosine, glucose and beef-heart infusion[86]. Semi-synthetic media will only support good yields of toxin when supplemented with beef heart infusion. For some, although not all strains of *Cl. tetani*, the concentration of iron in the medium would appear to bear an important relationship to toxin production, good yields of toxin being obtained only when the concentrations of iron is held within strictly defined limits. In the casein digest and beef-heart infusion medium of Mueller and Miller yields of toxin ranging from 2 to 8 $\times$ 10^5 mouse M.L.D's per ml. may be obtained[97].

Pickett, Hoeprich and Germain[97], using a highly toxigenic strain of *Cl. tetani* and a casein digest, beef-heart infusion medium, isolated a highly purified preparation of the toxin by a modification of the cadmium chloride precipitation method of Eaton and Gronau[47]. The final product contained 43 $\times$ 10^6 mouse M.L.D's per mg. of nitrogen and the total nitrogen calculated as protein constituted 100 $\pm$ 2% of the dry weight of the preparation. The toxin was finally obtained in pure crystalline form in 1946 by Pillemer, Wittler and Grossberg[103], the second bacterial toxin to be crystallized. The method for purification and crystalization of the toxin involves fractional precipitation with methanol at low temperatures under rigidly controlled conditions of pH, ionic strength and protein concentration. Crystallization of the toxin occurs slowly at $-8°$ C. under the conditions of preparation; the crystals disentegrate rapidly at temperatures above $-5°$ C. and dissolve in the mother liquor at temperatures above 0° C. The crystals dissolve instantly, at low temperatures in 0.15M acetate at pH 6.5.

Crystalline tetanal toxin is a protein with an estimated molecular weight of 67,000 to 68,000[15,73] and contains 15.7% nitrogen, 0.065% phosphorus and 1.04% sulphur[95]. The percentages of 13 amino acids in the protein have been determined[45]. There is nothing in the analysis of the molecule which might explain its toxicity for nerve tissue, although it is noteworthy that tetanal toxin contains exceptionally high percentages of aspartic acid and lysine compared to other proteins. The aspartic acid content is about 50% greater than that of leucine, a relationship that is also seen in type A botulinum toxin[27] but one that is the reversed in nontoxic proteins of known composition.

Among the lethal poisons known, crystalline tetanus toxin ranks second only to botulinum toxin, having a potency of some 75 $\times$ 10^6 mouse M.L.D's per mg. of nitrogen and symptoms of tetanus may be produced in the mouse with as little as 0.000013 gamma of the crystalline product[101]. There are rather marked variations in animal species in their susceptibility to the toxin; man and the horse are said to be among the most highly susceptible.

Upon standing at 0° C. or when treated with minute concentrations of formalin tetanus toxin undergoes toxoiding which would appear to involve polymerization of two toxin molecules which have a sedimentation constant of 4.5 Svedburg Units to a dimeric compound with a sedimentation constant of 7 S[99,102]. It is suggested that condensation occurs through the toxic groups leaving those radicles responsible for antigenicity unimpaired. The implication of this phenomenon as a possible explanation of the fundamental basis of toxoiding in other bacterial products is obvious.

THE MODE OF ACTION OF TETANUS TOXIN. Tetanus toxin acts centrally upon motor nerve cells of the spinal cord and medulla and peripherally at cholinergic nerve endings. The signifi-

cance of a peripheral effect of the toxin is not clear at the present time.

Theories concerning the pathway by which the toxin reaches the central nervous system have been the subject of much controversy over a period of many years. At the turn of the century Marie[77], Marie and Morax[78] and Meyer and Ransom[80] formulated on the basis of a series of ingenious experiments the theory of nerve carriage. It was concluded that tetanus toxin is absorbed by the end organs of motor nerves and travels in a centripetal current along the axis cylinders to the cord. The phenomenon of local tetanus, which develops first in groups of muscles injected with toxin, supported the axis cylinder theory of toxin transport. If the toxin were to travel directly along motor fibers of the area, it would be expected that the first cells of the central nervous system to be affected should be those anterior horn cells giving rise to the fibers and innervating the muscles of the area; subsequent diffusion of toxin throughout the cord would then give rise to the progressive development of generalized tetanus. It was noted that if the motor nerves to a limb were severed before the injection of toxin into a limb, the denervated leg failed to develop the spasms of tetanus. Similarly, if antitoxin was injected into the sciatic nerve on one side prior to the injection of toxin into both hind limbs, tetanus developed within a few days and commenced in the unprotected leg, whereas the protected leg failed to show signs of tetanus at any time. Toxin absorbed into the blood stream or injected intravenously was said to gain access to the central nervous system only after having been absorbed by motor endings.

The theory of axis cylinder transmission of tetanus toxin has been vigorously challenged by Abel and his co-workers[1,2,3,4,5,6,54]. Abel *et al.* postulate a dual action of tetanus toxin, a central and a peripheral effect which may be recognized as distinct physiological entities. It was shown that the injection of very minute amounts of toxin distributed to various parts of a limb induces purely local tetanus characterized by sustained muscular rigidity independent of external stimuli and with none of the reflex excitability seen in generalized tetanus. This is said to be the peripheral effect resulting from fixation of the toxin on motor nerve endings. The application of toxin directly to the cord, in the region of the anterior horns, produces only reflex spasmodic activity of the muscles supplied with impulses by the motor nerve cells of the area, with none of the persistent rigidity of local tetanus. The injection by any route of a full lethal dose of toxin gives rise to the full picture of generalized tetanus, that is, the paroxysmal reflex motor spasms which may be induced by various stimuli, the central effect, and the superimposed muscular rigidity which is sustained at all times, the peripheral effect.

On the basis of their experimental studies Abel and his colleagues concluded that tetanus toxin is not carried along the axis cylinders to the central nervous system but rather that it reaches the anterior horn cells by way of lymphatic vessels and the blood stream. They objected to the theory of axis cylinder transport on both anatomical and physiological grounds, and noted that when doses greater than a minimum lethal dose were injected into a limb that a high proportion of the toxin could be demonstrated in the vascular and lymphatic systems whereas they failed to demonstrate, at any time, toxin in the axis cylinders. It was further stated that the injection of a sublethal dose of toxin directly

into the sciatic nerve does not give rise to tetanus if precautions are taken to prevent leakage of the toxin into the surrounding tissues.

Since the appearance of local tetanus was not observed when toxin was injected into a limb after the section of the regional motor nerve supply, earlier workers insisted that functional connection with the spinal cord was essential to the development of tetanus. However, Harvey[61] claimed that if toxin was injected into a muscle soon after a nerve had been cut that local tetanus was produced and that it did not disappear until the motor nerve endings had lost their transmitting function; local tetanus could not be produced once the nerve had undergone degeneration. Harvey felt that the determining factor in the development of local tetanus was the integrity of the motor nerve endings and not the connection with the spinal cord.

The foregoing investigations have by no means settled the controversy concerning transport of the toxin. Friedemann[56], Wright[128,129], Baylis[13] and their colleagues have in more recent years presented convincing evidence that tetanus toxin may be carried to the central nervous system by nerves. Transection of the spinal cord in the lumbar region prevents generalized tetanus and death from an otherwise lethal dose of toxin inoculated into a lower limb or sciatic nerve[13,56]. If toxin is injected into a cranial nerve, as the vagus, the sequence of development of localizing symptoms suggests a radial spread of toxin from the motor nucleus of that nerve to neighboring motor nuclei[128]. It is reported, in agreement with the findings of early investigators, that toxin injected into the calf muscles of the rabbit may be identified in the sciatic nerve[13] and chemical sclerosis of the sciatic nerve proximal to the level of injection of toxin is said to impede the transport of toxin and prevent the development of local tetanus[13,129]. Friedemann and his colleagues[56] noted some years ago that some eighty times more circulating antitoxin was required to protect an animal from death when toxin was administered intramuscularly than when the same dose of toxin was given intravenously, which suggested that a high proportion of the toxin must reach the central nervous system by some route other than the blood stream.

We know little as yet about the mode of action of tetanus toxin on nerve tissue. The little information that we do have, and that largely of a negative nature, has been based on studies of peripheral effects or peripheral end results.

From a study of muscular responses in local tetanus Harvey[61] concluded that the phenomenon of local tetanus resembled in some respects the early changes seen in denervated muscle, and in other respects the changes occurring with eserine poisoning, and might be explained if one were to assume that the toxin acted at motor nerve endings in such a way as to result in an abnormal leakage of acetylcholine and at the same time a diminution of cholinesterase or a depression of cholinesterase activity.

Ambache, Morgan and Wright[9] have studied the effect of tetanus toxin upon the rabbit's iris. There are clinical features of tetanus, rather overshadowed by the more dramatic skeletal muscle spasms, which suggest that parasympathetic nerves may be involved in the toxemia. The injection of a small amount of toxin into the anterior chamber of the rabbit's eye is followed after a latent period of 1 to 2 days by a persistent mydriasis, failure of the pupil to react to light and failure of the pupil to contract after simulation of the third nerve, all indicating

that in this form of local tetanus cholinergic transmission to the sphincter pupillae is almost completely paralyzed. The response to oculomotor stimulation is partially restored by the instillation of eserine into the conjunctival sac, a fact which suggests that the toxin interferes with humoral transmission. Quite in contrast to Harvey's hypothesis of increased production of acetylcholine, Ambache *et al.*[9] show that the acetylcholine content of an intoxicated iris falls gradually to a concentration of about 50% of that of the normal eye and that of the aqueous humor to some 15 to 25% of the normal. It is doubtful if the diminished secretion of acetylcholine is due to any effect of the toxin on the enzymatic acetylation of choline. Torda and Wolf[119] found, if anything an increased synthesis of acetylcholine *in vitro* in the presence of all but very large doses of the toxin and Schaefer[109] states that the toxin has no effect upon the enzyme choline acetylase.

The experiments of Ambache and his collaborators lend support to the contention put forth by Harvey that the phenomena associated with local tetanus resemble in certain features the after-effects of denervation of skeletal muscle. Doses of carbaminocholine, a stable mimetic analogue of acetylcholine, that are insufficient to produce any effect in the normal control eye cause a marked myosis of the iris of the intoxicated eye. It is known that cholinergic effector systems become more sensitive to acetylcholine and parasympathomimetic drugs after their innervation has been destroyed[30].

The possibility that tetanus toxin might affect the cholinesterase content of tissues or depress cholinesterase activity, has been examined by various workers[9,10,67,79,109,120,125]. The little evidence that exists that cholinesterase might be inhibited by tetanus toxin is derived from *in vitro* studies where no distinction appears to have been made between "true" and "pseudo" cholinesterase. Thus Labenz and Genuit[67] reported that, *in vitro*, tetanus toxin was a potent cholinesterase inhibitor, whereas others have been unable to support this claim[10,67,120,125]. There would appear to be no diminution of cholinesterase content of the spinal cord in local tetanus[79] or in brain and cord in generalized tetanus even where large doses of toxin have been employed to induce the toxemia[98]. Martini, Torda and Zironi[79] studied the cholinesterase equivalents of affected muscles in local tetanus in rats with equivocal results, and Ambache and his colleagues[9] reported that there was no indication that the concentration of cholinesterase of smooth or skeletal muscles was diminished by tetanus intoxication. Due regard was given to total cholinesterase, "true" cholinesterase and "pseudo" cholinesterase. In this respect the effect of tetanus toxin would appear to differ from that of nerve degeneration where the concentration of cholinesterase undergoes a considerable decrease.

Although a good deal has been learned about the physiological end-results of tetanus toxemia, the manner in which the toxin induces such disturbances is still unknown. Peripherally, at least, the toxin would appear to be fixed at cholinergic nerve endings or possibly in the course of terminal unmyelinated fibrils proximal to the acetylcholine release region since, although there is a diminution in the production of acetylcholine *in vivo*, the toxin appears not to depress the enzymatic acetylation of choline. It is suggested that the decreased release of acetylcholine might be secondary to some derangement in transmission of the impulse proximal to the acetylcholine release region. Whatever the exact

site of action, fixation of the toxin on peripheral nerves produces physiological disturbances resembling in some ways those accompanying the post-traumatic degeneration of nerve. It is worthy of note that the period required for complete recovery in local tetanus is within the range of time required for repair of a crushed nerve, in marked contrast to the situation in local botulism. Localization of the central site of action specifically to motor nerve cells is largely the result of clinical observations of reflex motor activity or observations of such activity when toxin is directly applied to the anterior horns. Harvey[61], on the basis of the observed peripheral effects of the toxin, raises the question as to whether the action is on the motor nerve cells *per se* as is usually thought, or upon synaptic endings of fibers in relation to nerve cells.

As in botulism, the derangement of function in tetanus would appear to have a purely physiological background. Animals which succumb to tetanus intoxication, regardless of the severity or the duration of the illness, show no specific morphological changes in nerve or other tissues[101].

Pappenheimer has suggested, on the basis of the characteristic latent period seen in experimental tetanus toxemia and the extraordinary potency of the toxin, that it might act not as an enzyme or as an enzyme inhibitor but rather by interfering with the synthesis of some enzyme system concerned in nerve function. It is possible that normal neuromuscular relationships might be upset by an interference with the energy-yielding biochemical reactions that are vital for normal nerve and muscle metabolism. However, Pillemer and Muntz[100] were unable to detect any affect of crystalline tetanus toxin upon the *in vitro* glycolysis in mouse brain homogenates, or upon adenosinetriphosphatase activity of nerve and muscle tissue of animals poisoned with massive doses of toxin.

It has been repeatedly suggested that tetanus toxin might not act directly on nerve tissue but rather by producing in the body some secondary substance responsible for the symptoms of tetanus. This was first postulated by Courmont and Doyon[34] who claimed to have isolated a strychnine-like material from tetanic muscles. This would account for the failure of tetanus antitoxin to neutralize fixed toxin; although tetanus antitoxin possesses a high protective value before the toxin reaches nerve tissue, it has little or no effect upon the course of the toxemia once the toxin has combined with nerve, even when applied before the onset of symptoms[127]. However, investigation has failed to confirm the existence of such a substance in poisoned nerve or muscle[56,100,101]. The toxin has a remarkably high affinity for nerve tissue, so much so that it is neutralized by fixation to nerve such that the combination is no longer toxic for animals, although intact toxin may be recovered from the mixtures with washing[57,123]. It would seem that some component of nerve tissue has a higher affinity for the toxin than has antitoxin.

A number of authors[8,9,45,60] have stressed points of resemblance between tetanus and botulinum toxins which are of more than trivial interest. The toxins are produced by closely related species of the one genus, *Clostridium*. Both are proteins the elemental and amino acid constitution of which provide no clue to the high degree of specific neurotoxic activity that they exhibit. They have essentially the same qualitative composition of amino acids and both show in common certain peculiarities in the relative proportions of some of the amino acids as contrasted with other proteins of known compo-

sition. Both toxins exert an effect in the region of cholinergic nerve endings resulting in a diminished output of acetylcholine, despite the fact that neither substance depresses the enzymatic acetylation of choline. Although the clinical pictures in botulism and tetanus do differ on the whole, a preliminary excitatory period is not infrequently seen in botulism, and in tetanus paralytic symptoms such as ophthalmoplegia and lingual and facial paralyses may occur at times. It is quite possible that the active groups of these two neurotoxins may be closely related.

Diphtheria Toxin. Some form of paralysis occurs, as a late complication, in from 10 to 20% of all cases of diphtheria, ordinarily making its appearance in the second or third week of convalescence. The muscles of the soft palate are the most frequently affected; ocular paralysis in some form is usually seen and at times the pharynx, the diaphragm and the muscles of the extremities may be involved. In severe cases respiratory paralysis due to involvement of the phrenic nerves may result in death. In cases that survive, complete recovery of muscle function ensues within a matter of 2 weeks.

PROPERTIES OF DIPHTHERIA TOXIN. The growth requirements of *C. diphtheriae* have been fairly well defined and it is now possible to obtain good yields of diphtherial toxin, such as 1000 guinea-pig lethal doses per ml., in semi-synthetic media consisting of acid hydrolysates of gelatin or casein supplemented with certain amino acids, vitamins and salts[84,96], or in semi-synthetic media composed of pure amino acids, ammonium sulphate, trace metals, inorganic salts and vitamins[40]. The concentration of iron in a culture medium bears a critical relationship to the production of toxin[95]. Maximum toxin production occurs only over a narrow range of iron concentration, with an optimum of about 0.1 gamma of iron per ml. Further additions of iron, although improving growth, result in a progressive decrease in toxin production and when a concentration of 0.5 gamma per ml. is reached, toxin is no longer produced.

Diphtheria toxin has been isolated and characterized by Eaton[46], Pappenheimer[92] and others[74,87,106]. The purest preparation obtained by Pappenheimer was a heat-labile protein with an isoelectric point of pH 4.1 and an estimated molecular weight of about 72,000[99]. The purified product contained 16.0% nitrogen, 0.75% sulphur and less than 0.05% phosphorus. The minimum lethal dose of purified toxin for the guinea-pig was approximately 0.001 mg. The toxin contained 2100 to 2400 Lf per mg. of nitrogen and 30 guinea-pig M.L.D's per Lf. By the application of gel-diffusion methods, Pope and his colleagues[105], in 1950, showed that the purest toxin preparations available at the time contained a number of distinct antigens. Thus Pappenheimer's preparation showed a total of fourteen distinct lines in the test. Pope and Stevens[106] have since reported the isolation of a crystalline protein with both *in vivo* and *in vitro* properties of diphtheria toxin which gives a single line in agar diffusion tests and contains 3200 Lf per mg. of nitrogen. It would appear despite crystallization and a very high degree of purity that even this preparation is contaminated with a desoxyribonuclease[104].

THE MODE OF ACTION OF DIPHTHERIAL TOXIN. In contrast to tetanus and botulinum toxins, diphtheria toxin would appear to be for the most part nonspecific with respect to the tissues that it attacks. The lesions take the form of cellular degeneration with edema and hemorrhage and may occur in any of the tissues of a susceptible

animal. There is no general agreement concerning the distribution and nature of the nerve lesions which account for the paralytic forms of diphtheria. The available evidence suggests that degenerative changes of a nonspecific character involve the nerves associated with the paralyzed muscles and take the form of an ascending peripheral toxic neuritis. Histologically the changes are similar to those of Wallerian degeneration seen following division of a nerve but are rarely so severe or complete.

Whether separate "classical" and neurotoxic molecules are produced by *C. diphtheriae* has been, in the past, a matter of some dispute. The matter could be resolved readily by studies of experimental toxemia employing the purified toxin preparations now available; unfortunately experiments concerned with the neurotoxic action of diphtheria toxin have been performed with crude whole culture filtrates. Ehrlich[51] noted that, although guinea-pigs rarely developed neurological symptoms when inoculated with the toxin alone, when toxin-antitoxin mixtures were employed in which the toxin was not completely neutralized, paralysis was readily induced provided that the animal survived beyond 8 or more days. Neurotoxic action of such sub-neutral filtrates was attributed to the presence of "toxones" which were said to possess a lower affinity for the antitoxin than did the toxin which produced classical symptoms. Ehrlich believed the "toxones" to be specifically neurotoxic in action and distinct from the classical toxin. Dreyer and Madsen[39] claimed, on the other hand, that toxin-antitoxin mixtures, which produced only paralysis in guinea-pigs, functioned as the classical toxin in rabbits. It is known that, while the guinea-pig develops paralytic symptoms only after the administration of subneutral toxin-antitoxin mixtures, these symptoms appear in the hamster following the administration of suitable quantities of toxin without the addition of antitoxin[89]. Presumably the guinea-pig is so highly sensitive to the general tissue lesions induced by diphtheria toxin that unless the toxic culture filtrate is sufficiently neutralized, the development of paresis is forestalled by death of the animal. The specific reaction of the hamster may be explained by its relatively low susceptibility to the classical action of the toxin.

On the basis of our present knowledge, it seems reasonable to conclude that diphtheria toxin is a single substance with a relatively low affinity for nerve tissue as compared to other vital tissues of the body.

The mechanism by which diphtheria toxin produces lesions is not clear. Pappenheimer *et al.*[91,93,94] suggest that the toxin may interfere with cellular oxidations. As has been noted, toxin is secreted into the medium only when the level of iron in the medium is reduced to a low level. A porphyrin is found in culture filtrates only when the iron concentration is reduced and its production parallels the secretion of toxin. The addition of iron to the culture medium in concentrations above those optimal for toxin production results in the disappearance from culture filtrates of the porphyrin, iron and diphtheria toxin in a molar ratio of 4:4:1. All of the iron added over the range in which toxin production is exhibited can be found in the cells in parallel with a corresponding increase of the iron containing respiratory pigment cytochrome b. Pappenheimer has suggested that diphtheria toxin might be the protein moiety of cytochrome b, which in the absence of iron cannot be incorporated into the complete cytochrome molecule, and that the toxin might act by blocking the synthesis of mammalian cytochrome b or some

closely related enzyme in the susceptible animal. Yoneda and Pappenheimer[130] have shown in the past year, however, that a toxigenic strain of *C. diphtheriae* and a nontoxigenic strain from which the former had been derived by infection with temperate bacteriophage β behave in the same manner in their relationship to the iron content of the medium. With low concentrations of iron the yields of protein and porphyrin are the same for both strains, but toxin is not a component of the protein fraction secreted by the nontoxigenic strain.

Shigella Dysenteriae "neurotoxin." In common with other members of the Genus *Shigella*, *Sh. dysenteriae* contains a heat stable endotoxin which appears to be a complex of, or identical with, the well recognized somatic antigens. The endotoxin is a thermostable protein-polysaccharide-lipoid complex[17,18,19,81,82,83]. Injected parenterally into rabbits, mice or guinea-pigs the endotoxin causes diarrhea with inflammation, hemorrhage and necrosis of the intestinal tract. The pathological lesions closely resemble those found in clinical cases of bacillary dysentery.

In addition to the endotoxin, *Sh. dysenteriae*, unlike other organisms of the group, produces a thermolabile toxin commonly referred to as an exotoxin, despite the fact that all evidence points to its release only upon the autolysis of the cells[17,18,19,20]. The exotoxin is produced only by rough variants of the organism. This substance induces well defined paralytic symptoms in rabbits and mice, a fact which has led many observers to class it as a neurotoxin.

Shigella neurotoxin is obtained in highest yield when the iron concentration of the medium is reduced to below 0.03 mg. per L.[41]. In the elaboration of diphtheria toxin the toxin would appear to be secreted as a waste product when there is not sufficient iron present for the complete synthesis of cytochrome b. However, in the production of the *Shigella* neurotoxin the reverse would appear to be true. As long as the iron is quantitatively converted into bacterial heme it does not inhibit the elaboration of toxin. It is only when the organism accumulates iron that is not incorporated into heme that there is an inhibition of toxin production[62].

Highly purified preparations of the neurotoxin have been obtained by various procedures[11,41,52,53,63]. The most potent preparation has been obtained by van Heyningen and Gladstone[63] in an electrophoretically homogeneous state. It is a protein containing some 15.7% nitrogen. The purified preparation contained 750 LD 50's per mg. for each kg. of mouse by weight and 1,150,000 LD 50's per mg. for each kg. of rabbit by weight.

Unlike the endotoxin, the neurotoxin of *Sh. dysenteria* may be toxoided with formalin to produce an effective antigen. Boroff[20,21], on the basis of immunological studies, has suggested that the protein neurotoxin is simply the protein component of the somatic antigen. Both the R and S variants are said to produce this protein but the S form incorporates the protein into the protein-polysaccharide-lipid endotoxin complex, whereas the R form fails to do so.

Since the earliest observations that two toxic fractions were produced by *Sh. dysenteriae*[55,88], there has been much controversy concerning the existence of a specific neurotoxic activity of the exotoxin. Although degenerative changes had been noted in ganglion cells of some animal species, neurological lesions could not be induced in all species nor did it appear that the action of the toxin was entirely specific, since it produced changes in

parenchymatous organs, vasoconstriction and capillary hemorrhage. Even in those animal species which have a high degree of susceptibility to the neurotoxic activity of the exotoxin, this toxin would appear to have a relatively low affinity for nerve tissue *per se*. It appears that the pathogenesis of *Shigella* neurotoxin depends on dissemination of the toxin by the blood stream, and rabbits and mice actually survive longer when toxin is injected into the blood stream than when it is injected directly into the medulla oblongata[65]. There is no evidence that the toxin can be transported in nerve trunks, nor does it exert any effect on peripheral nerve endings[65].

The multiplicity of toxic constituents in crude preparations complicated the efforts of investigators to evaluate the separate activities of the enterotoxic and neurotoxic fractions. Within recent years this problem has been resolved through the use of the purified neurotoxin prepared by van Heyningen and Gladstone[63]. Employing pure toxin in their studies, Bridgwater and his colleagues[24] have concluded that the toxin has no specific affinity for nerve cells proper and that damage to nerve tissue is mediated through primary damage to the endothelium of small blood vessels. The intravenous injection of lethal doses of purified neurotoxin in rabbits is followed by the appearance of focal hemorrhages in the grey matter of the spinal cord enlargements which develop some time before the animals present clinical signs of neurological origin. Degenerative changes in neurones of the spinal motor muclei are not seen until some hours after the development of the focal hemorrhages and are definitely related to the distribution of the affected vessels. As Cavanagh *et al.*[32] note, the profound neurological effects observed in rabbits has tended to obscure the fact that intestinal changes are frequently present in rabbits inoculated with the neurotoxin. Employing purified neurotoxin, they confirmed Bridgwater's observation that the exotoxin acts essentially on blood vessels, although there is considerable species variation in susceptibility of the vessels of the central nervous system as compared with those of the intestine and other areas of the body. Nervous lesions occur in mice and rabbits but none in other species as rats, hamsters and guinea-pigs. Edema and hemorrhages in the gastrointestinal tract occur regularly in rats and in rabbits with high doses, whereas the hamster shows only edema of the lungs and pleural effusions, and guinea-pigs are completely insusceptible to the toxin. All of the diverse lesions are believed to have a basic vascular origin. It is doubtful, then, if *Sh. dysenteriae* exotoxin can be regarded as a neurotoxin in the strict sense of the term as we apply it to botulinum and tetanus toxins. The significance of the so-called neurotoxin in the human disease is by no means clear. Paralytic or other distinctly neurological complications are an exceedingly rare occurrence in dysentery caused by *Sh. dysenteriae* and, apart from the severity of the illness, the dysentery caused by this organism does not differ clinically or pathologically from that due to other members of the genus.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

JOHN E. GORDON, M.D.
PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY
HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH

AND

THEODORE H. INGALLS, M.D.
ASSOCIATE PROFESSOR OF EPIDEMIOLOGY
HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH
BOSTON, MASSACHUSETTS

MEDICAL ECOLOGY AND THE PUBLIC HEALTH

BY JOHN E. GORDON, M.D.

(From the Department of Epidemiology, Harvard University School of Public Health, Boston, Massachusetts)

BIOLOGY as a scientific discipline has departed broadly from its interests of some decades ago, and in more or less opposite directions. The smaller and smaller parts of a functioning organism are one concern; the other is with aggregates of individuals as they constitute a society of animals, of plants or of men. Medicine has followed a similar course.' Epidemiology thereby has gained increasing recognition as a means for better understanding of health and disease in man. Concerned basically with groups, epidemiology complements clinical and laboratory study. The purpose here is to trace the development of human ecology, and the influence it has had on epidemiology as a diagnostic discipline in operational public health and in health research.

The early biologist was content with study of the intact organism: its description, its classification and what it did. The museum of natural history was at the height of its vigor; the herbarium and the botanical garden were the counterpart in botany. Then about a hundred years ago came the unifying generalization[107] that all living things were composed of cells. As a consequence the search turned to the mechanisms and to the nature of the life process itself.

The Minutiae. The mainstream of interest in an enlarging biology has been toward increasingly minute fractions of living things, or of the substances which act upon them; first to organs and systems, then to tissues, to cells, to molecules, eventually to the atom and now its nucleus. This succession has influenced the methods of biology; it also has brought the biological sciences into the midst of social, political and economic activities of nations everywhere.

The shift is more than from natural history to the laboratory. The biological laboratory itself has changed materially, so much so that spectrophotometers, equipment for measuring radioactive and high energy sources, the electron microscope, and materials for chroma-

tography are as common as the scalpel and the dissecting microscope of other days. An able observer[102] of the scientific scene remarks that one is hard put to it to guess whether he is looking in at physics, or chemistry, or biology.

There is no implication, however, that understanding of the living organism is to be resolved into physicochemical detail on a molecular level[65]. The living organism furthermore has substance, which makes necessary an environment if it is to function; behavior without reference to other organisms is not understandable, in the matter of food for one thing[9]. These two considerations are mainly responsible for the second and rather opposite direction which biological activities have taken.

The Wider Horizon. To know the behavior and activities of an organism, necessity requires that it be related to the universe of which it forms a part. Living things are to be viewed in relation to others of their kind, to creatures of other species, and to the physical environment which is the habitat of all. This need is reinforced by appreciation of the common nature of living things that came from Schwann[107]. It is enhanced by recognition of the interdependence of species, the one on the other.

Ecology as a division[134] of biology has responsibility for exploring the mutual relationships between various living organisms of a universe and their animate and inanimate surroundings[124]. The emphasis is on total environment, the sum of the external forces, appreciating that preceding knowledge of ingredients always aids in judging the effects of a mixture. The more pertinent consideration is that environment is often a composite and sometimes a compound.

Housing[141], for example, may be viewed as a physical feature of the environment, a matter of rooms and roofs and toilets; or as a social influence by reason of the resulting density of inhabitants, or propinquity to favorable or unfavorable influences; or again as a psychologic determinant in respect to morals, ethics, or industry. To the extent that housing bears on health and disease, the concern is not so much with the individual parts of the environmental complex, as with the relationships between them and how the resultant whole affects man. No rigid line exists between animate and inanimate environment. The practical considerations were recognized by Sydenstricker[116], in stating the impossibility to measure with absolute precision the influence of any one host characteristic or any one environmental factor, even though it be a major one, without knowing with equal accuracy the influence of the other factors.

Ecological Units. The unit of observation in ecology is a group of living things within the natural environment, in contrast to other situations of a single organism or some one of its constituent parts. More than anything else, this distinctive feature marks ecology as an independent activity. Three ecologic groupings are distinguished, according to increasing complexity: a population, a community and an ecosystem.

In all three the group is conceived, not as a simple aggregate to be examined piece by piece, but as an entity[44] resolved into a whole through organization and integration of its parts. As such, it functions as a unit and for practical purposes is an organism of itself, capable of adapting to its environment and to the stresses which arise from within its structure[80]. It has a history of origin, and experiences growth, youth, maturity and senescence. As a functioning organism it has characteristics common to the individuals[86] from which it is formed but

often differing in degree and extent. Traits such as density, dispersion by emigration and immigration, an intrinsic rate of natural increase, age distribution and mortality are restricted to groups. A population has powers and potentialities not present in any of its components[18]. An influence on one part is commonly felt throughout[62].

Of itself, the single organism enters into the basic concepts of ecology only to the extent that it is an essential premise to the existence of a population; the population is the fundamental feature. In field work, however, the individual organism often serves a practical purpose as a unit of measurement.

For a time, workers in plant ecology[12] supported a division of interests, whereby the group approach was recognized as synecology and distinguished from autecology. Autecology was defined as study of the adaptions made by an individual organism throughout its life history. These matters seemingly are more the business of the general physiologist and the animal psychologist. Ecology is now generally accepted[62] as the study of living creatures in the plural and in relation to their surroundings.

A similar parallelism between individual and group approach is seen with clinical medicine and public health, both concerned with the same general affairs but with distinctive interests and separate methods. The individual person may be cured of syphilis, or may become immune to measles. He may be dying of starvation and yet is not permitted to steal, use violence or murder in order to get food. A population on the other hand rarely becomes free of syphilis, or wholly immune to measles. It may be well fed while individuals starve, and with little compunction may resort to war and pillage in order to prosper. These differences between the health, social attitudes and diseases of the individual and those of the group of which he is a part give direction to the objectives and the practice of clinical medicine as contrasted to public health.

Recognition of the medical problems of the individual is by clinical diagnosis, mainly of a sick person, with the aim to remedy a specific and current condition. The problems of the community are identified through epidemiology[47e], by ecologic analysis[47c] of populations which contain both the sick and the well. The concern is with situations then existing and also with those to be anticipated, thus with both health and disease in their mass manifestations. Public health, as interpreted by Haven Emerson[35], is the application of the sciences of preventive medicine for social ends, with the aim not primarily to salvage the individual but to understand and reduce sickness of any kind in a community or group.

Populations. Population refers to multiples of a single kind of living thing. Such a group more properly could be called a society. That is not common usage; indeed, lack of common practice in terms used is a general defect in the various fields, social and biological, where ecologic methods and interpretation find application. Some of the confusion arises from conflict between vernacular and technical use of a word, but technical workers by no means agree[118], as the glossary of ecologic terms by Carpenter[14] well illustrates.

A concept of plant or animal populations is as logical as that of human populations; it depends where interest centers. Closely associated species, such as man and his parasites, are sometime referred to as a mixed population. Something less than the whole of populations in a given area may be viewed as a multiple species population. Human populations have frequent

specific designation as mass or herd or crowd, thus used by Greenwood[53] in epidemiology; as flock, school, swarm and numerous others for animals; or a stand in relation to plants.

The Biotic Community. A community or the more explicit phrase "biotic community," is the accepted designation[18,72] for the total of living things within a specified universe. A population thus refers to numbers of a single species; a community is inclusive, embracing all populations of an area, both plant and animal, and including man. The biome[18] and also biocenose as advanced by Möbius[87] are suitable, but neither has had wide acceptance.

Anthropologists, many other social scientists, practicing physicians, and public health workers, because their interests center on man, commonly use community in the vernacular sense as applying to a population of people living in a particular place. This is reasonable and suits their activities. In human ecology, however, such a community of people must be understood as no more than a part of a larger union which includes all living things, the biotic community. The larger complex is the unit of observation in ecological interpretations. The interactions and interdependencies of species make it so.

Even the most inconsequential plant or animal fails to live in isolation, whether considered singly or in its group aspects. Because of the need to meet food and energy requirements, to seek protection from enemies, and support from allies, its reactions are understandable only in reference to other organisms. Competition and cooperation run throughout the universe of living things. The result is not a series of discrete population units but an association of populations of many kinds, a total ecologic complex, the biotic community.

The Ecosystem. For a given time and place, all animate and inanimate things blend into an organizational pattern of one kind or another, upon which depends survival and well being of the living creatures within that universe, and also the character of the environment itself. The integrated whole is the ecosystem. It is the most complex development among ecologic arrangements[77], which now have been traced from individual, through populations and communities to the ultimate ecosystem. The outstanding characteristic of the ecosystem is its dynamic behavior. The relationship between things and living beings is consistently moving, shifting, changing.

The world into which a man is born is not the world from which he departs, perhaps less patently so in Victorian times than now, but still an enduring law. All living things, possess an infinite capacity for variation[139]. As elements of an ecosystem, the included populations and communities adapt to a habitat and the habitat adjusts to them[30b], as Shelford[109b] illustrates in the fluctuations of non-forest animal populations in the upper Mississippi basin. This is no more than the reflection of a biologic law[124], the balance of nature. It holds for individuals and for individuals as a group[30a].

The tendency to uniformity or stability in the normal body states of man as an individual (internal environment or fluid matrix) has been defined by Walter Cannon[13] as homeostasis. It is in direct analogy with what has just been described for the external environment and communities. The knowledge has been turned to such practical applications as the physiology of heat regulation and the science of clothing[89].

The major variations to be observed among populations are in numbers, in ecologic position or dominance in the particular universe, and in changes of

species characteristics as related to an accompanying evolution or regression. The relationships of the moment, the causes determining them, and the direction of their movement are the main concerns of ecologic investigation.

The competition of populations and the effects of environment lead to ecologic successions[34], whereby a population changes and develops in a variety of directions, sometimes to gain ascendancy over another and sometimes indeed to replace it. Some variations are short term and repetitive, according to season[62]. Annual changes are common. Others are long term and often profound, the true biotic succession. Succession is an orderly process, as outlined for plant communities years ago by Cowles[24]. Presumably it holds for all living things. The satisfactory end is in a climax stage where the relation between organism and environment is stabilized at a state of essential equilibrium favorable to both.

With realization that ecosystems are dynamic and never wholly static, the expectation is that the ecologic climax is far from indestructible. A new influence introduced into the system or an old one eliminated can disrupt the established balance and set off a new succession whose ultimate end is difficult to predict. Such influences may be of natural origin. In these days of technological advance they are commonly man-made, occasionally through direct intent but more frequently as the accidental or unexpected result of some completely foreign motive.

The ecosystem is an integrated whole; a change in some one constituent sets the potential for readjustment of all others. What happened when the European rabbit was introduced into Australia is well known, in respect to agriculture and to the general economy. The results of recent attempts to regain the former equilibrium by eliminating the rabbit are not yet complete. The virus of myxomatosis, a microorganism highly fatal to rabbits, was introduced artificially[40]. The early results were remarkably successful. The rabbit population fought back, however, through adaptation. Where the climax will be established remains to be seen; the advantage thus far is with man. The biological and social aspects of the experiment are fascinating.

Man is an integral part of a biotic community and as such clearly susceptible to the laws of succession. Many of the changes in his environment are of his own doing, but the anticipated result is just as definite as when it comes about through natural forces. In 1900, the ten principal causes of death in the United States included six infections. The top two were of that nature, tuberculosis and pneumonia. Currently there are only two infections in the list, tuberculosis still the most prominent but ranking no better than sixth. The degenerative and neoplastic diseases along with deaths by accidental injury are now the leaders. Death rates for pneumonia have decreased; those for carcinoma of the lung have increased. Attention centers now on deaths of the aged, in place of deaths in childhood.

The control of communicable diseases in man brings the principle of biotic succession fully into play. The present generation of physicians has seen a part of an ecologic succession which began many years ago, whereby scarlet fever in this country has changed from a disease of appreciable fatality and long disability to one of far less consequence. Its history shows repeated such instances, and so does that of diphtheria. The frequency of inapparent infections in scarlet fever and diphtheria[85] is evidence of the ability of host and infectious agent to adapt.

Mumps struck an ecologic climax at least 2500 years ago. Its present clinical and epidemiological behavior is that which Hippocrates described.

Herpes comes close to being the perfectly balanced host-parasite reaction. The virus attacks man almost universally, establishes itself permanently, but produces no clinical manifestations except through a disturbance of homeostasis, as by excessive exposure to heat or the presence of another infection. The results then are inconsequential, in the form of fever blisters; serious injury is close to a curiosity.

On the other hand, the disastrous consequences of adding a new element to a long established equilibrium are seen in the epidemic of cholera in Egypt[110] in 1947, of plague in Burma[97] during World War II, and perhaps most strikingly when poliomyelitis invaded an Eskimo population[96] in northern Canada.

Too often man assumes that he can manipulate nature freely and without consequence; hence the grand effort to wipe out disease. Within 10 years Ceylon brought about a remarkable reduction in malaria, an infection that had prevailed throughout its history. The resulting increase in population, as analyzed by Cullumbine[25], was scarcely within the calculations of the original design of operations. Malaria is only one of many infectious diseases where control has resulted in population problems[52] that measurably reduce the primary gain.

An equally weak assumption is that once a communicable disease is wiped out it will stay wiped out. That view is against natural history. The favorable situation may prevail with continued effort, but sooner or later accidents are rather certain. Truly remarkable progress has been made in South America in the control of yellow fever. Whole districts have been freed from the disease, especially the seaports which were once the primary foci. In the inner recesses of the continent the disease persists endemically as jungle yellow fever. Goiaz State in Brazil is an area in which jungle yellow fever had been adequately controlled by an active vaccination campaign, with no cases for 6 years. A sizable immigration of susceptibles served to light up the smouldering infection and produce some 2000 cases, a circumstance described by Soper[113] under the challenging title of "The Elephant Never Forgets."

Historical Evolution of Ecology. An understanding of ecologic principles is favored by examining the origins of ecology[133] and its subsequent development. The usual difficulty is encountered in determining just where ecology had its beginning. For almost any idea, sufficient diligence and a willingness on occasion to add a little speculation will bring out scraps of information in the oldest of records. The source of that information to the man who made the record is something else; perhaps it was original, more likely it was not. At any rate, an event ultimately comes along so definite that it stands as a landmark. Darwin's publication[27] in 1859 on the *Origin of Species* serves this purpose for ecology. Darwin himself[28] credits the earlier work of Malthus[82] on human populations as aiding him in arranging his ideas; and incidentally that ecologic problem still outdistances all others as an influence on human health and welfare[52].

The demonstration of variation in organisms, and of the limiting action of environment, left clear implication that life and environment need to be studied together. The sciences of genetics and ecology were a natural outgrowth. They divide interests in a common effort to define the behavior of man, his survival and his numbers[8];

ecology concerned with external factors, genetics with internal. Genetics has developed the more rapidly, primarily because that discipline is better suited to laboratory investigation under controlled conditions. Field study has been the main reliance in ecology; it is costly, time consuming and controls are difficult. So far as medical ecology is concerned, the laboratory approach has been little used: this in relation to populations as the experimental unit[54,138] and distinguished from investigation of individual factors, which of course has been extensive and by a variety of biological sciences.

Plant Ecology. Ecology began as a biological discipline. The German botanist, Ernst Haeckel[57], published in 1870 the first formal statement of concepts and principles, namely that the structure and behavior of organisms are significantly affected by their living together with other organisms of the same and other species, and by their habitat. He gave the name ecology to this direction of study.

Subsequently, Scandinavian workers led by Eugenius Warming[136] took a solid hand in developing plant ecology, with contributions on plant geography and physiological plant anatomy. The beginning of American thought in ecology is reasonably traced to Cowles[24], the University of Chicago botanist. Aside from contributions to plant ecology he was instrumental in arousing interest in animal ecology, a subject which has had strong emphasis[2] ever since.

The stimulus to a concept of plant ecology came out of early descriptive studies of vegetation, specifically plant geography. It became apparent that various environmental factors affected plant growth. This led to measurement and evaluation of soils, their water content and the effect of light, temperature and rainfall.

The next step was to correlate these several influences with responses in vegetation, from which came information that plants influenced one another in growth qualities; that life in a highly organized plant community, such as the forest, was materially different from that of a plant growing alone. The second generalization was that all manner of living things influenced plant life, from the microfauna and microflora of the soil to plant parasites, insects, earth worms, rabbits, other herbivora, and most of all man himself.

As knowledge of these relationships increased, attention centered on special aspects, such as physiologic, physiographic and geographic plant ecology. Accumulating facts eventually permitted generalizations beyond direct considerations of plant life and plant growth.

Disease of plant communities came to be recognized as one of the results of the continuing interplay between a population and its environment. Some were common to all plant formations or plant communities of a climatic area[137]. Others were a function of subdivisions, gradually recognized as plant associations, consociations and societies; groupings which are translated with no great effort into the families, neighborhoods and communities that characterize man.

In providing the food for animals, plants largely dominate, modify and delimit the environment[108a] of animal populations. The extermination of a plant species, a depletion of soils, deforestation, the introduction of harmful plants or animals[122] easily leads to repercussions on man himself, variously biological, social, economic and even political. The plant predators, the bacteria, have a decided influence on the welfare of animals.

Animal Ecology. A good many years passed, however, before the principles

of group behavior of plants were turned to similar problems among animals. The charming little book of van Beneden[132] on *Animal Parasites and Messmates* which appeared in 1885, and the studies of Möbius[87] on oyster culture were distinctly ecological; but the start of an animal ecology may be said to date from 1913 when Adams[1a] published his *Guide to the Study of Animal Ecology*. The pioneer work of Shelford[109a] on animal communities in temperate America appeared the same year. Thereafter came solidification of principles[38a] closely paralleling those of plant ecology, but modified by differences in subject matter, notably the capacity of most animals to move about. Allee *et al.*[2] have brought these principles together so well that attention is restricted to three fields of animal ecology which relate directly to the public health of people.

Arthropods. Many species of arthropods, mainly insects, have an important place in the community health of man through ability to act as vectors of infectious agents. In repeated instances, control of the resulting communicable disease in man is through control of the vector, other measures being secondary. In this endeavor, entomologists for years have followed ecological methods, with the result that ecological thought runs through present day entomology to a greater extent than for most other biological sciences. Marston Bates[8a] has even used the mosquito as a pattern to define ecologic concept and principle.

The entomologist Uvarov[131] was one of the first to recognize the sameness of epidemiology and medical ecology in stating that the epidemiology of most insect pests and measures for their control must be carried out from the ecological point of view, through recognition of the injurious insect as an integral part and even as a product of its environment; that to prevent epidemics the conditions accompanying and causing them must be known.

All ecology is brought into play in the new problems arising from modern insecticides[64]; for one thing, the ability of flies, lice and mosquitoes to adapt in nature to these products. The failure of the Sardinian project[78], directed toward eradication of vector mosquitoes from that malarial island, illustrates the practical difficulties in attempt to manipulate nature.

Animal Parasites. The relation between animals and their parasites is especially suited to establishing the ecologic determination of disease. The efficient parasite, as brought out by Swellengrebel[115], does no harm to the host by its presence, nor to itself. Under other circumstances, the association is mutually advantageous, the phenomenon of symbiosis. The rabies virus, by contrast, is no parasite at all, but a predator because it must kill its host to survive. Efficiency in adaptation, and the extent to which evolution is induced, determine the eventual result[5]; sometimes as a balanced parasitism, and at others an increased pathogenicity of the agent. In his theme of human factors in parasite ecology, Cort[22] finds the social behavior of man not particularly to his advantage in attaining the desirable status of the efficient host. The predator-parasite-symbiont situation is thus an expression of ecologic theory, that the resultant of interaction between organism and environment is variously neutral, harmful or beneficial, thereby determining the dominance of species in a pyramid of life.

Ecology of Disease. Evidence that disease of living things is conditioned ecologically was greatly strengthened by a series of investigations by Charles Elton[33b], a pioneer British ecologist, on the relation of animal numbers to

climate[33c], on plague and the regulation of numbers in wild mammals[33a] and eventually a study of epidemic diseases among wild animals[33d]. He ended thus: "Ecology, and particularly that brand which deals with animal numbers, has a definite contribution to make toward the epidemiology of disease of mammals and also toward the solution of certain important problems in human disease." It is incidental that those investigations, when they appeared many years ago, were instrumental in directing me to interpret mass disease in man on ecological principles, mass disease being disease as it affects the general body of mankind, and as a consequence, to view epidemiology as medical ecology.

Human Ecology. Man scarcely could escape attention in an expanding ecology. In the first place, human populations enter into a multitude of ecosystems. Each population within a system has an ecological position, which marks its relative importance to other constituent members[125]. Since man is regularly the dominant population, he is hardly to be neglected in assessment of function and behavior of the system as a whole.

Secondly, man is subject to the same biological laws which control the destinies of other living things. He is dependent upon other organisms for immediate survival and for maintaining environmental conditions under which continued existence is possible. Ecological interpretation of his problems would appear as reasonable as for any plant or animal.

Finally, among social animals that quality has far and away the highest development in man. Social relations imply a consideration of groups and group reactions, which is the special province of ecology.

A human ecology came considerably after animal ecology, and indeed as a development of relatively recent years. Its progress has been favored by the apparent variety of interests inviting attention. Advance has been inhibited by the greater complexity of man as an organism, and by the many kinds of environment in which he chooses to place himself. The ability to make that choice is of itself an outstanding characteristic.

Man as an Organism. The chief feature which distinguishes man from other animals is an ability to reason, and through his intelligence determine what he does to himself and to his environment. An unusual flexibility in adaptation also contributes, although in public health it seems to take three kinds of workers for reasonable accomplishment: the physician to adapt man to his environment, the engineer to adapt the environment to man, and the social scientist to adapt men to each other.

Within limitations of biologic variation, man is a thinking animal and acts consciously to set up rules and laws of conduct and to establish formal organizations and institutions to his benefit[30b]. He has learning capacity, has developed language by which to transfer ideas and information, and has invented means of transport by which to move about. In essence, man has evolved a culture which exists only in rudimentary fashion in other animals. This enlarges his capacity for adaptation beyond the biological processes to which most plant and animal populations are confined. With culture as a mechanism, the quicker and easier social adaptation greatly surpasses that of the few other social animals, such as bees and ants, which are compelled to depend on instinct. Nevertheless, the culture of man must be geared to his biological needs, to the environment in which he lives, and to the technologies which he has originated. These matters,

along with his social instincts, make man a complicated subject for ecologic analysis despite the basic similarities[108a] between human and unmodified natural communities.

The Human Environment. Strictly natural communities are rapidly vanishing, communities such as I have seen on the high African veldt, zebra, impala, wildebeeste and others, feeding together of an evening and contributing to the common welfare by variously excelling in hearing, in smell or in sight. Natural communities which include man are close to a curiosity. If interpretation is not too strict they would include the Bushman[84] of Africa and isolated tribes in central India[81]. The communities which cover a large part of the earth are modified by man[123]. Increasingly they give way to wholly artificial communities, in the form of metropolitan areas and great cities.

Man's system of domesticated plants and animals[70], the technologies of modern industry, ambitions toward status beyond a blind struggle for survival, and a set of values unmatched by other species, all contribute to an environment to be defined in broader terms than for other living things. The human environment is thus conceived as of three main divisions[48]: the physical environment, the biological environment and the social environment.

The physical environment of man includes those factors of weather and climate, topography and geologic structure which act on all living things in determining survival. Ellsworth Huntington[69], the noted geographer, introduced a consideration individual to man, that a temperate climate of alternating seasons conditions the higher levels of civilization.

The biologic component of the human environment includes the universe of living things that surrounds man, all else than man himself. It is a major part of the total complex. The principal matter is of food chains[135], more of a consideration with man than with most animals because of the wide range from which he draws[3]. Agriculturalist and economist have special concern with this feature of human ecology, and of course the nutritionist.

The social environment, so outstanding a feature of human ecology, is that division which relates to the association of man with his fellow man. It has to do with such things as patterns of urbanization, housing, trends of migration, problems of minorities, delinquency, mental disorders and even political matters. The social environment, therefore, touches upon all manner of sciences connected with man. Some are biological, as those of medicine and public health, the social sciences expectedly, economics and others which include psychology, social and cultural anthropology and demography.

Space and area are organizational concepts in ecology[36]. The social environment complicates matters for the simple reason that administrative boundaries uncommonly coincide with the natural area of an ecosystem; the use of official data is made difficult. Problems associated with the social environment are frequently international, with the result that the ecologic concept of territory comes close to being planetary. The resulting universe of all mankind is decidedly unwieldy.

The social environment has a remarkable capacity to make problems difficult, especially when the social complex is that of metropolitan concentrations of people. That explains in a way the liking I have always had to observe population pathology in man[47] in rural regions. Conditions are simplified in the Arctic; in respect to people,

vegetation and climate. The Indian village[51] is about as close to a natural human community as one can get. The motivation is much of that once ascribed to Thoreau, the man who went to the woods because he wished to live deliberately and confront only the essential facts of life.

The many factors in the social environment of man, and the relation they have to so many elements of a science of man, led to a readily anticipated result[8c]. Human ecology developed in a variety of directions.

Fields of Interest in Human Ecology. Medical ecology has established a firm place within the structure of human ecology as a means for interpreting disease processes of man in their mass relationships[47c]. An ecology of health[23, 41] uses the same principles and methods. Banks[6] considers human ecology as the guide to practice of social medicine.

In scholarly fashion Barrows[7] as early as 1922 formulated ideas put forth earlier by Ellsworth Huntington[69] and a number of others, to present geography as the science of human ecology, the main concern the manner in which physical factors influence civilization[127]. He took pains not to deny to others the use of these principles in their separate fields. These ideas and the use of ecologic methods gained ground among geographers, so that White and Renner[140] came to interpret human geography as the ecological study of society.

The inherent nature of human ecology gives ready understanding that a sizable part of its activities are within the province of the social sciences. Park[92a] has the credit for the first systematic formulation of ecological principles applicable to social problems of the human community. His industry over the years[92b,93] led to a rounded conception of human ecology as it differs from plant and animal ecology, a position well stated by Hollingshead[68]. Some sociologists now tend to view human ecology as the individual concern of the social sciences[62], more or less restrictedly having to do with the nature and development of community structure[99]. Wirth[143] gives more consideration to biological features in recognizing human ecology as the spatial, temporal, physical and technological basis for analysis of areal social life. The most recent report by the United Nations[130b] on the world social situation reveals problems of a kind meriting use of ecologic methods by economists to a greater extent than heretofore[101], and presumably to the same advantage as for sociologists[26].

Ecological methods would appear suited to the social psychologist, for human behavior[146] touches closely on interaction with the physical environment, climate for instance; and human relations are in essence the resultant of intraspecies balance. This field has had less emphasis in human ecology[100] than others, but the problems are multiple: of delinquency, crime, and migration to name a few. Faris[37a] and numerous others have shown the connection with a developing epidemiology of mental disorder[50].

Human ecology as adapted to the purposes of the anthropologist shows a rather straight line development from natural history[8b], through the concepts laid down by Bews[9], to a social anthropology largely concerned with human conduct[8c], including land use and related interests. The mixture of biologist and sociologist so often found in anthropologists presumably accounts for the common interest[61] of epidemiologist and anthropologist in mass disease of man. The circumstance that both rely on ecologic principle in expanding their individual disciplines[121] has furthered that relationship.

A General Ecology. The evolution of ecology rather justifies the question as to how many ecologies there are. The extensive fission within human ecology gives reasonable query about its existence, particularly with such divergent sciences as geography and sociology claiming it as their own.

Unity of Human Ecology. A simple look at the interests just noted comes close to settling the question of an entity. Medical ecology for instance draws upon all others of those recorded in search for the causes of mass disease. Conversely, no one of the others can entertain serious conclusions about a specialized problem without consideration of health matters. All would appear to be aspects of a single science of man[139], considered in his group relationships.

Biologist and sociologist use the same general principles and employ the same broad methods in their approach to ecological problems. That objectives are different does not mark an independent discipline. In all science, parts of a subject commonly are studied to advantage because of special capabilities of the investigator or a selected interest. Nevertheless, respiratory physiology and neurophysiology are still physiology.

Man is an animal, and as Adams[1b] emphasizes, as definitely dependent on the physical, plant and animal world as any other animal, although in different degree. From this he reasons that ecological understanding begins with the biological generalizations derived principally from plant and animal ecology. Elaboration depends upon integrated effort by biological and social sciences. Marston Bates[8c] in recalling that a biological inheritance is still with man, believes a biological basis is essential to any concept of human ecology, recognizing at the same time that biological propositions must be examined anew in the cultural context.

Holistic Character. The holistic doctrine which underlies ecology gives answer to the question of one or many ecologies. Holism as proposed by Jan Christian Smuts[112], the distinguished South African statesman, soldier, botanist and philosopher, views life in all its manifestations as a single system in process of interaction with the inorganic environment. Observation sometimes centers on man, sometimes on environment, and sometimes on the interaction of the two, but interpretation is in terms of the whole[9]. Accordingly, plant ecology, animal ecology and human ecology, each with its numerous subdivisions, are specializations within the broader field[122], to be understood only against the background of the parent discipline.

Practical Approach. Operational feasibility commonly directs that one or more species be withdrawn from a community for special study, a plant, an animal and more often man. An individual interest may relate also to a fraction of the ecosystem where the concern is of forestry, fisheries, agriculture or natural resources[90], as a mountain, a pond or a field. A specific mass disease of man is frequently the attraction, or a social phenomenon as delinquency. Such specialization favors accumulation of factual knowledge. It is commonly enhanced these days by resort to laboratory analysis of material collected in the field, to define more clearly some separate feature of the organism or a factor of the environment. Conversely, field investigation often gives leads to fundamental investigation wholly aside from the immediate problem. The essential requirement is that findings be related to the ecosystem as a whole. The search for cause and effect is thereby facilitated. Usefulness to the community and ecologic understanding depend upon that synthesis.

It is apparent that much of the work

of ecology is done not by ecologists but by persons trained in some other skill and employing ecologic methods. Most problems relating to living nature merge into ecology, and hence require a variety of skills. Quantitative thought becomes necessary, if the objective is to determine the balance of forces, and so inevitably the statistician.

Laws of Ecology. The attempt now is to resolve the various ecologic concepts thus far considered into a statement of ecologic laws, conceived as extending through the life processes of all animate things as they constitute groups, to include man, wild beasts, the domestic animals, plants, pests and parasites. What follows is primarily to the credit of C. C. Adams. It came from an exchange of views in his book-beleaguered home in Albany, N.Y., subsequent to his retirement. Books and material on ecology almost literally oozed from the eaves, great stacks in every room and cubbyhole. I recall that we had to clear the kitchen sink of precious pamphlets and documents before we could make tea. At any rate, in that atmosphere we settled on four considerations conceived as applying generally.

1. All living things tend to produce more young than are needed to maintain the species. The resulting overpopulation, whether relative or absolute, brings into play a series of checks and counterchecks which dominates all biology.

2. A suitable food supply in adequate amount is the main factor in maintenance of a species. The relation to all other species of that environment is direct, since it resolves into so fundamental a consideration as enough to eat and yet avoid being eaten. It is a major check to overpopulation; it gives substance to such ecologic concepts as energy relationships, ecologic balance and species dominance.

3. The physical environment of a species, of which the important parts are water, temperature, oxygen and the opportunities for injury from frost, fire, flood and similar natural forces, must be suited to its well being. The primary concepts of variability of organisms, adaptation and evolution relate to this principle.

4. Maintenance and survival depend on interspecies relationships which permit survival from attack of natural enemies, variously free living organisms and those of parasitic nature. Associated concepts are those of competition and cooperation between species, levels of community organization, ecologic succession, species dominance, adaptation and variation.

A fifth law applies specifically to man and to human ecology.

5. Through his intelligence and by conscious effort man is able to control his environment to a remarkable extent. Culture, social structure of communities, species dominance, development of technologies and social adaptation are important related concepts.

The proposal now is to examine the application of ecologic principles and interpretation to the study and control of health and disease. So greatly does ecologic thought permeate the responsible discipline, epidemiology, that medical ecology stands reasonably in apposition.

Medical Ecology. Ecological principles apply to that part of medical practice concerned with disease in groups of people. Primarily that is public health; the family group, in the practice of preventive and social medicine, would be included. Ecology also is limited to group considerations; hence the fit.

Public health is fundamentally an applied science. In furtherance of its purposes it draws on an imposing number of sciences, sciences in the

sense of Conant[20a,20b]. The range is through physical, biological, medical and social disciplines to include even the earth sciences.

Mainly because of this, public health requires a science of its own by which to give background for conceptual ideas on the interactions of man and his environment in determination of health and disease. That science has equal obligation to originate methods by which to test such ideas, methods expectedly unique in that the subject is a group. Human ecology would appear suited to the purpose because of its content and its unifying character[10,66], provided it is viewed in the broad sense of both biological and social components, and with emphasis on medical ecology, namely, epidemiology.

The foundation for an ecological interpretation of health and disease in man came from Theobald Smith[111] in his *Parasitism and Disease*, and from Edgar Sydenstricker[116] writing on *Health and Environment*. The concept took practical and direct form in contributions by Strong[114] and by Dudley[31], to be enlarged by ecologic analysis of specific infections, as malaria by Hackett[58], typhus fever by Zinsser[145] and plague by Meyer[86]. Just as epidemiology originated in the communicable disease, so did ecologic interpretation.

The community studies of pellagra by Goldberger *et al.*[46] were developed ecologically; that influence has increased progressively among nutritionists, as reflected in recent work by Trulson *et al.*[129]. It has extended to chronic noninfectious disease[145], to traumatic accidents[47a] and to so many individual diseases of these classes as not to warrant cataloging.

In this progress the physical environment has had the attention that would be expected, and similarly the biologic environment. The notable addition to the content of epidemiology under the influence of ecology is in relation to the social environment. Motivation toward control of disease is itself of social origin; sometimes fear, sometimes altruism and sometimes economic need. What may be done is as often determined by economic considerations as by existing technical method or knowledge of causality.

The world community becomes more closely knit by reason of social habit, transport and communication, with the result that the protection once afforded by isolation and distance disappears. Agreement among epidemiologists is general, that such social factors as agricultural practices, population dynamics, political and educational systems, living habits, occupations and technologies, and role and status in the community, have a strong part in causality of community disease. The universal decline in mortality from tuberculosis is presumably due as much to altered social conditions as to specific control measures.

Throughout history, factual knowledge and its quantitation have failed to keep pace with conceptual idea. This holds for social factors in disease causation. Within past weeks, I attended a conference on air pollution, a man-made health problem if there is one. A member of the conference with sufficient reputation to take the risk asked what are these socio-economic factors we are talking about. The silence that followed was impressive.

The fitness of the environment of which Henderson[63] spoke, clearly calls for strong attention to the social component. A considered scheme for field investigation of social factors in health and disease, as interrelated with biological elements and with acceptable means for measurement, is an immediate practical requirement of medical ecology.

Perhaps the most important gain in an interpretation of epidemiology as medical ecology is recognition of multifactorial causation; that whether or not a *sine-qua-non* exists in the form of a specific agent of disease, the total pattern of causality tends to vary from one situation to another, from time to time and from place to place. The principle was stated for biology many years ago by Jennings[70]. The practical deduction is that programs for prevention and control, although logically based on principle, must be tailored to the particular circumstance. The concept of epidemiology as medical ecology is now summarized.

Epidemiology as Medical Ecology. Basic ecologic theory serves well in the interpretation of infectious processes. The contending species in communicable disease of man are a host and an agent of disease[142]. That one is free living and one is a parasite does not alter the situation, any more than that one species is animal and one is plant, that one is large and the other small, or that one is powerful and dominant among living things, the other dependent and weak. Communicable disease is no independent relationship set apart from other life processes, nor are its problems a law unto themselves. The infectious process is a part of biology, another of the resultant effects of an impact between a living organism and its environment. The environment is complex and many sided, with physical, biological and social components[48]. As such, a disease entity is the result of no simple contact between a host and an agent of disease. A great variety of environmental factors have a part in its origin, and a balance of affairs determines the issue.

The frequency and behavior of one disease commonly determines what happens with another[119]. Additionally, few localities are sufficiently isolated these days that they remain unaffected by the movements of disease in adjoining regions. Many infections with established predilection for one host have a valency permitting spread to others. Even when restricted to a single kind of host, an outbreak can have far-reaching effect on the well being of other species, including man, through serious disturbances of established nutritive, economic and social attributes. The epidemiologic problems of plants, of animals, and of man are considered to advantage as parts of a single discipline. An understanding of the world behavior of a disease is often necessary for satisfactory interpretation of the problems of a restricted universe.

These features have led to a conviction that an ecologic interpretation offers greatest promise in defining the behavior of infection and of infectious diseases acting on groups of people. Epidemiology, which has to do with these matters, thus becomes a part of human ecology; specifically, medical ecology. Health and disease, like the fundamental matters of existence and survival, are thereby interpreted as the results of an ecologic interplay which is variously particular, continuous, reciprocal or indissoluble. Disease in animals, in plants, in any living thing, is looked upon as a maladjustment between the host and the existing environment.

If communicable disease is a pure ecologic process, its aim is that of all biologic processes, namely to permit survival of both living elements. Nature is as much concerned with the welfare of the parasite as with that of the host. This has an important bearing on principles designed to guide prevention and control. The practical objective is not so much to eradicate disease as to modify it to innocuousness.

A wide range of conditions is in-

cluded within modern ideas of population pathology[47f]. The approach to problems of the communicable diseases has been through epidemiology. The indication is for an extension of these methods to the wider field of usefulness[47b]. Practicability depends upon the assumption that all mass disease and injury conforms to the same laws of ecology as do communicable diseases.

Granted that an etiologic interpretation of disease and injury is the basis of modern medical thought, then the agents that give rise to pathological conditions must be variously viable and nonviable, sometimes transmissible and sometimes not. If morbid conditions of man are the result of a reaction between man and his environment, then all disease conditions can be interpreted in terms of three principal factors: an agent, separated from environment for convenience of interpretation and understanding; a host, the injured or affected organism; and the broadly defined environment, in which both host and agent exist, itself entering strongly into the interaction between the two. In the absence of a known or definable agent, the basic system of man opposed to environment serves usefully. Thus looked upon, all disease and injury in their group manifestations are interpreted as ecologic phenomena and amenable to the methods of epidemiology.

Beyond the matter of survival, the health of a population represents a dominance of positive adaptations to its particular environment, either through greater numbers of positive than negative adaptations, or because they are more heavily weighted. Otherwise the organism can scarcely endure. Disease from the standpoint of man is an unfavorable resultant of the forces of ecology, the extent and seriousness of which depend on the kind of balance, the nature of the biologic equilibrium currently existing. In other circumstances, the social equilibrium of the human population is the critical consideration. Commonly both are involved. The anticipated behavior is dynamic.

The practical work of medical ecology is to determine how biotic balance and social equilibrium are established and identified; how they are maintained, once achieved; and how disturbed, together with the mechanisms involved in transition to another stable order. Unfavorable adaptations as they occur are assessed in terms of the clinical nature of the disease that results, the number of persons affected, and the places and duration of the process. The favorable adaptations that lead to health offer more difficulty.

A working program for ecologic analysis has been presented in another place[50] and Gordon, Leavell and Ingalls[49] have placed epidemiology, medical ecology, in the general scheme of public health practice by which community health problems are solved.

Ecological Manifestations in Mass Disease. Brief illustrations of how these principles of medical ecology enter into selected problems of the moment are now presented.

Antibiotics. The introduction of antibiotics was followed promptly by a lesser fatality for many infectious diseases. The period of communicability was shortened, with the result that fewer foci of infection existed at a particular time. Spread of infection was thereby limited, to such extent that the authoritative manual on *Control of Communicable Disease in Man* of the American Public Health Association[21] recognized a new principle, the sterilization of human reservoirs of infection by early antibiotic treatment, and modified its recommendations accordingly.

However, the inexorable forces of biologic law came into play. From the

standpoint of the environment, microorganisms adapted to what for them were new surroundings. Some of the original gains were lost. A new compound may relieve the situation, but potentially is subject to the same fate.

The human host also took part in the ecologic interplay. The antibiotics, interceding in the pneumonias so often the terminal event in cancer, cirrhosis of the liver or other chronic disease, permit more advanced stages of these conditions. A social factor is thus introduced, the need for providing expensive medical care over longer periods to a nonproductive fraction of the population.

Population Dynamics. In countries where overpopulation is most acute, the immediate cause traces rather directly to the medical profession. The remarkable gains of recent years in reducing death rates, while birth rates remain at the established and previously necessary high levels for population maintenance, could have no other result than significant increase in numbers. No geographic area is overpopulated except as numbers relate to the carrying capacity of that environment[144] and the demands of the particular human culture. Overpopulation thus involves the economist and the sociologist along with the agriculturalist, the geographer, the anthropologist and others[79]. The demographer evaluates the situation; the sociologist and the biologist, which includes the agriculturalist, are called upon to do something about it; and the competition for resources brings in the political scientist[108c].

The menace of overpopulation is the central problem for mankind, at present and certainly for the coming century; it has important medical components. In terms of man's existence, overpopulation is of relatively recent origin, somewhat more than 200 years during which the world population has quadrupled. Previously, population numbers had tended to remain stable; changes were slow[75] because the means to alter the basic conditions determining them were poor. An onrushing culture and civilization have changed all of that.

An ecological view of the population problem[42] can be said to have begun with Malthus[82], which is in accord with the initial interest of ecology in numbers. The ecologic concept took form with the work of Carr-Saunders[15] who interpreted the population problem as a study in human evolution. Kingsley Davis[29a,29b] brought out sociological realities. Coale and Hoover[19] have clarified economic relationships, while Taeuber and Balfour[117] made a comprehensive analysis of the population problem in Japan.

The diminution of infectious disease as a curb on population increase puts the burden on the other two main determinants[130a], war and famine. The compensating action of a program of contraception appears necessary to meet an urgency not to be left to social and economic adjustment, which is long term and costly in its realization. The cultural obstacles standing in the way of the rapid adoption of contraceptive practices are formidable. The practicability of their use by a population as contrasted to individuals is largely untested.

Both social and biological components enter into population problems of man, as can be attested from personal experience[120]. The two are sometimes so intertwined that attempts to separate them are fruitless. The principle[11,126] is worth recalling that biological elements oftentimes are examined to advantage in animal populations[126], thereby freeing a characteristic from the social influences that confuse the issue in man. Indeed, Pearl[95b] did that

preliminary to his extensive studies[95a] on the natural history of human populations.

Mental Disorder. A continuing progress in public health has cleared away enough of the preoccupation with physical illness to uncover a substratum of mental disorder more impressive than most physicians expected. That result is not surprising. The central nervous system of man evolved under conditions of a simple community life close to nature. The complexity of the modern environment progressively increases, to such extent that adaptation becomes more difficult, and when successful often leaves evidence of residual strain, especially for certain personality types. These realities suggest ecologic methods of analysis as specially suited to the mental disorders. The limited progress in etiology furthermore warrants all available methods of study, to include epidemiological methods as well as those of laboratory and clinic.

Clinicians tend also to adopt an ecologic viewpoint, both in civilian[55, 103] and in military practice[59], which has been fostered by the American Psychiatric Association[4] through publication of a diagnostic and statistical manual.

The work of Faris and Dunham[38] in Chicago in 1939 gave impetus to field investigation of populations, which both workers have enlarged in subsequent years[32a,32b,37b]. Schroeder[106] confirmed the Chicago results of a prevalence of mental disorder greater at the center of cities and progressively lesser rates toward the periphery. Such observed geographical differences indicate something more than an inherent psychic or physical constitution as involved in causation. Attention turned toward spatial distributions according to social and economic status[128], culture tracts and complexes[17], the family setting[43] and a variety of other factors of the physical and social environment[83]. Queen[98] among others emphasizes the extent to which epidemiological investigation supplements case studies. With benefit of methods[74] originating in general study of chronic and noninfectious disease, ordered surveys of mental disease have been made in both urban[94] and rural populations[104], as yet too limited to permit generalization. These basic observations on time-place-person relationships are just being turned to causality, with search for etiological factors in such conditions as schizophrenia[67,91], suicide[105] and mental deficiency[71]. Epidemiological investigation of mental disorders gives indication of increasing activity, with the National Institute for Mental Health taking a lively part[39]. Progress suffices for considered opinion about control measures[56] on a population basis, with the evident implication of some idea about cause.

Ecology and the Public Health. Instead of gathering together now the various principles of human ecology in a relation to public health, the choice is to place emphasis on three features; one relates to the practice of public health, a second to education and training, and a third to research in health matters.

Practice of Public Health. A direct result of applying ecological principles to the practice of public health is to require of a medical discovery or a new technology something more than an assessment of its direct worth before accepting it as a public health measure. The decision ordinarily depends upon a measured gain toward a defined objective: either lesser risk of death, decreased residual defect or shortened disability, to include also attention to side effects, operational difficulties and probable acceptance by the public. The evaluation is essentially clinical.

An ecologic analysis requires that the procedure be judged against the total health structure of a community[88]. Whenever a factor is added to an ecologic system, or subtracted from it, the expectation is a rearrangement of remaining elements to give an altered character to the whole, frequently beyond the direct influence of what was introduced. This is not always favorable. New health problems sometimes arise, as serious as that which was remedied. Old ones may take new form, or change significance. Such variations sometimes appear promptly; or with equal significance evolve over long periods. Other effects on society may outweigh health considerations. The need, therefore, is an estimate of net gain to the community rather than the gross value of the particular procedure.

An ecologic evaluation consequently calls for value judgments as well as scientific insight, especially those peculiarly available to the scientist or public health administrator by reason of his professional competence. The eventual decision will be made by society, with aid from other interests touched upon, but the professional health worker has a potential share not possessed by others; and along with that an obligation to contribute to the culture in which he is working. To those who lament mixing science and sociology, the issue may as well be faced: public health is both a social and a biological activity. If the label be that of philosophy, others[60] join me in attesting to the respectability of that association with biology.

Education and Training. If the concept of an ecological determination of mass disease is valid, the required education and training in human ecology as part of a preparation for medicine and public health may be summarized cryptically. Some few should know a lot about it and all should know something. Four classes of students presumably are involved: the future expert in medical ecology, the general public health worker, the specialist in individual biological or social sciences, and the medical student.

The growing demand for more epidemiologists, those highly skilled in the principles of medical ecology, has been met to a considerable extent by the recently instituted specific fellowship program of the United States Public Health Service; the schools of public health of the country provide the necessary facilities.

Whether general education in public health takes the form of more highly technical courses of instruction, or a primary emphasis on principles and background, a framework is revealed around which to build the desired curriculum. This fundamental required course would be concerned with the nature and behavior of populations of people, and with methods for identifying and measuring medical problems on a group basis. Human ecology, viewed in the broad sense, would seem innately suitable as a start, because of its unifying feature in bringing together biological and social sciences. A subsequent emphasis on epidemiology represents a natural progression in ecologic thought to specific matters of health and disease. Because ecology and heredity combine to control development and behavior of man[108b], human genetics would have a prominent place, along with biostatistics to provide quantitation and the principles of public health practice to assure productive application. These opinions are neither wholly personal, nor academic; they are supported in principle by prominent public health administrators[73].

For reasons to be developed, instruction in human ecology and something of its subdivision, medical ecology,

should be available at the graduate level to students specializing in sciences relating to man.

The place of epidemiology as the foundation for instruction in preventive medicine for medical students has been accepted by medical educators[16] and is the guiding theme in current texts[76]. More emphasis on general ecology, along with its special interests as expressed through epidemiology, would initiate the broader principles at a more advantageous time than at the graduate level.

Health Research. Among applied sciences, public health draws to an unusual degree on knowledge from many disciplines, each important in its own right but alone presenting a highly sectarian viewpoint. Interrelating and synthesizing this information to the uses and understanding of mass disease is a necessary concern of public health. The complexity of the main unsolved problems of the day requires something more than the public health investigator making use of information from other fields. A common participation in work in the field and in the laboratory is frequently desirable. I have expressed my pessimism of interdisciplinary team endeavor in research[47d] as contrasted to its success where the objective was development or operational procedure. A main drawback to accomplishment would seem to be lack of a common basis for understanding. Because of its nature, human ecology is believed to provide that medium. The recommendation of graduate instruction in ecology as a part of preparation for work in sciences connected with health and disease was for that reason.

The kind of studies which cross existing departmental lines presumably would be facilitated by ability to view events in the perspective of human environmental relationships. The common endeavor should not detract from realizing the potentialities of a special discipline; indeed, activity could be aided through recognition of leads to studies within the special province.

The chief contribution of an ecological viewpoint in public health would appear to be its unifying influence, the bringing together of the biological and social sciences in a concerted attack on what are common problems.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF DECEMBER 17, 1957

The Fixed Charge Hypothesis for the Mechanism of Bioelectric Potentials. GILBERT LING, PH.D. (Eastern Pennsylvania Psychiatric Institute, Philadelphia). In an earlier communication (Fed. Proc., 14, 93, 1955) evidence was presented to show that the mechanism of cellular resting potential is closely similar to the mechanism underlying the potential of a glass electrode, which, however, classically had been thought of as a physicochemical model for the Donnan type of membrane potential, held to be responsible for the origin of cellular potential as well. The experiments of Horovitz and of Haugaard, and the practice of using glass bulbs filled with Hg as pH electrode, pointed out that the glass electrode potential is determined only by H^+ ion adsorbed on a microscopic thickness on the glass surface. A kinetic analysis of a new K^+ ion equilibrium reached after varying external K^+ ion concentration and the time course of potential change following such a variation of external K^+ ion shows that in muscle cells, the resting potential also bears no direct relationship to the macroscopic intracellular K^+ ion concentration but is related only to the surface K^+ ion concentration. Further evidence in support of this concept was obtained from studies of collodion membranes, which since L. Michaelis has been a favorable material to illustrate the Donnan type of potential with mobilities of ions through the collodion membrane as determining factors in the effect an ion has on the size of potential. Just as glass electrode was at one time supposed to be permeable to H^+ ion and impermeable to K^+ ion and consequently sensitive as H^+ electrode; the higher K^+ ion permeability through collodion membrane as compared with Na^+ ion was supposedly to the basis for a comparatively greater K^+ ion sensitivity of dried collodion membrane electrode. A current theory of the cellular electrical potential rest on similar attributes of cell membrane and the cellular potential is thought of as dependent upon the permeability (or mobility) of ion through it. We have shown, however, that a glass electrode, sensitive only to H^+ ion and insensitive to K^+ ion could be converted to an electrode sensitive only to K^+ ion and insensitive to H^+ ion by simply coating it with a thin layer of collodion, no more than a few μ in thickness. The experiments showed that the bulk of the membrane and ionic permeability through it bears no essential relationship to the measured potential at all, and that it is the surface adsorbed cation that determines the electrode potential and the selective adsorption of a cation determines the selective ionic sensitivity.

Some Interrelationships Between Anesthetic Action, Ion Movement, and Membrane Potentials. A. M. SHANES, PH.D. (National Institutes of Health, Bethesda, Md.). Unidirectional fluxes of sodium and potassium in the sciatic nerve of *Bufo marinus* have been studied in the usual way by measuring the uptake or the release of the radioisotopes by this tissue. The effect of 0.1%

cocaine on influxes differs substantially from that on outfluxes. Potassium influx is depressed to about the same absolute amount whether it has been previously reduced to about 1/3 by metabolic inhibition (oxygen lack ± iodoacetate) or not. This depressed influx remains roughly constant in cocaine for at least 4 hours in the metabolically uninhibited preparation, but the outflux undergoes only a transitory decline, returning within 2 to 3 hours almost to the original level. In inhibited nerves, however, in which potassium outflux is 50% greater than in uninhibited preparations, the anesthetic causes a sustained suppression of this 50% increment in outflux; eletrical measurements show that such action on the augmented potassium outflux of inhibited nerves is due to a depression of enhanced sodium influx, which is responsible for the accelerated potassium outflux during metabolic inhibition. Sodium outflux in uninhibited and inhibited sciatics is unaffected by the alkaloid. The significance of these findings for the mechanisms of cocaine action and of passive and active transport of sodium and potassium ions are discussed.

The Different Varieties of Electrogenic Membranes. HARRY GRUNDFEST, PH.D. (Department of Neurology, College of Physicians and Surgeons, Columbia University, New York). A considerable body of data supports the conclusion formulated a few years ago[1], that there are two fundamentally different kinds of electrical activity in excitable tissues. The classifying characteristic is the mode of their responsiveness and that difference gives rise to different constellations of other properties[2].

The commonly recognized variety of electrogenic membrane is that which occurs in axons and in many kinds of muscle fibers. Its response is initiated by a depolarization of the membrane. This last may be produced by an applied stimulus, or may be intrinsically generated by the local circuit of an already active region. The dominant response of electrically excitable membrane is an all-or-nothing spike, which is decrementlessly propagated. Electrical excitability therefore is admirably suited to conductile funtions.

Reception and transduction into electrical terms of information reaching sense organs, or the synaptic inputs of postjunctional cells is mediated by electrogenic membrane that is not electrically excitable. Therefore reception by most sense organs leads to a depolarizing "generator potential" which can be graded in proportion to the strength of the stimulus and maintained while the stimulus lasts. This activity in turn operates upon adjacent electrically excitable, conductile membrane to excite impulses in the latter according to a number-frequency code determined by the interacting properties of the two systems. Synaptic transmission is mediated by a depolarizing postsynaptic potential which also acts upon adjacent electrically excitable membrane. This electrogenesis, too, can be graded and sustained.

Electrical inexcitability implies obligatory nonelectrical transmission, which in the context of neural mechanisms means that transmission involves release of a chemical agent from the presynaptic terminals. Thus a functionally complete neuron has an electrically inexcitable input, a conductile, electrically excitable section, and a secretory output. These components may be anatomically distinct or not, depending on the particular tissue. Several varieties of electrically inexcitable electrogenic cells are also known in which conductile activity is missing.

The differences in electrogenic mem-

branes have a number of implications for cell functioning and provide an electrophysiological basis for neuropharmacology[3]. Phenomena such as Weddensky inhibition and diphasic excitatory-inhibitory actions of drugs are accounted for by these differences. Electrophysiological and pharmacological concepts stemming from recognition of these different properties have also been applied with considerable success to the analysis of electrocortical activity, and of the modes of action of synaptic drugs.

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BOOK REVIEWS AND NOTICES

PEACEFUL USE OF ATOMIC ENERGY. VOL. 10. RADIOACTIVE ISOTOPES AND NUCLEAR RADIATIONS IN MEDICINE. Pp. 544; illustrated. New York: United Nations, 1956 (Columbia University Press). Price, $8.00.

THE International Conference on Peaceful Uses of Atomic Energy, held in Geneva during August, 1955, was the first truly international meeting held on the subject of atomic energy. Some 1,050 papers were presented at the Conference and have been published by the United Nations. Topics of direct interest to workers in medicine are published in Vol. 10 and Vol. 11.

Volume 10 contains four excellent articles which deal with the general applications of radioisotopes in biology and medicine. These are followed by a group of twenty-seven papers which are concerned with therapeutic uses of radioisotopes. The remainder of the volume consists of fifty-four articles on the use of various radioactive substances in the diagnosis and study of disease.

The discussions are written by workers from all parts of the world, well-known in their respective fields. Accordingly, there is to be found in this volume an important reference text for physicians, radiologists, biochemists, biologists and others interested in therapeutic or metabolic uses of radioactive isotopes. C. Z.

PEACEFUL USE OF ATOMIC ENERGY. VOL. 11. BIOLOGICAL EFFECTS OF RADIATION. Pp. 402; illustrated. New York: United Nations, 1956 (Columbia University Press). Price, $8.00.

THIS volume contains sixty-three papers concerned with the biological effects of radiation which were presented at the International Conference on the Peaceful Uses of Atomic Energy, at Geneva, Switzerland, in August, 1955. The articles are grouped under the following headings: Biological Effects of Radiation, Modes of Radiation Injury, Carcinogenesis and Metabolism of Bone-Seeking Isotopes, Effects on Reproductive System and on Fetus, Mechanisms of Radiation Injury, Protection and Recovery, Genetic Effects: Human Implications.

These papers are authored by investigators from all parts of the world and present an excellent summary of information referrable to radiation injury. From this volume and its companion, Vol. 10, one may obtain a comprehensive understanding of the impact of the atomic era on medicine. Accordingly, both volumes are recommended not only to those who deal directly with radioactive substances in clinical and research medicine, but to all physicians and workers in allied medical fields. C. Z.

THE NATURE OF BRUCELLOSIS. BY WESLEY W. SPINK, M.D., D.SC. Pp. 464; 56 ills. Minneapolis: University of Minnesota Press, 1956. Price, $8.00.

THIS is the most complete and best presentation of the subject of brucellosis that has yet appeared. There are chapters on the Brucella Cell, The Reservoir of Brucellosis, The Dissemination of Brucella Organisms from the Animal Reservoir, Epidemiological Studies on Human Brucellosis, Pathogenesis, Natural Course, Complications, Diagnosis, Therapy and Prevention. There are presented protocols of 244 cases from the author's own experience. There is full coverage of current views and knowledge of the subject in veterinary medicine, and there are cited 906 references. The book is highly recommended to all physicians. R. K.

CHALLENGES TO CONTEMPORARY MEDICINE. BY ALAN GREGG, Vice President Emeritus of the Rockefeller Foundation. Pp. 120. New York: Columbia University Press, 1956. Price, $3.00.

ONE of the great medical philosophers of this century has here recorded some challenging ideas for physicians to ponder. These are the titles of the five chapters of the book: How Dear is Life?, What is the Meaning of Disease?, Current Factors Affecting Medicine, How are Medical Education and Medical Care Best Paid For? and The Natural History of the Doctor. Every physician should read these last messages from a pen that death has stilled. R. K.

BIOCHEMICAL INDIVIDUALITY. THE BASIS FOR THE GENETOTROPHIC CONCEPT. BY ROGER J. WILLIAMS, Professor of Chemistry, University of Texas. Pp. 214; 17 ills. New York: John Wiley & Sons, Inc., 1956. Price, $5.75.

In this stimulating book, the author has drawn attention to the high degree of individuality which is present at physiological and biochemical levels. Dr. Williams challenges the commonly accepted view that humanity can be divided into two groups: (1) the vast majority who possess attributes which are within the normal range; and (2) a small minority who possess attributes far enough out of line to be considered deviates. Indeed, using the 95% level as the line of demarcation between normal and abnormal for one character, only 0.902 would be normal with respect to two measurable items, and 0.60 (0.95^{10}) and 0.0059 (0.95^{100}), respectively, would be normal with regard to 10 and 100 uncorrelated items. Hence the author's hypothesis that practically every human being is a deviate in some respect.

Having stated this hypothesis, Dr. Williams discusses the genetic basis of biochemical individuality. This is followed by consideration of anatomical variations and their significance, individuality in composition, of enzyme patterns, of endocrine activities, and of excretion patterns. Various pharmacologic manifestations, individuality in nutrition, and miscellaneous evidences of individuality are also described. The remainder of the volume consists of a discourse on the genetotrophic approach, and discussion of its implications for biological sciences, medical and dental research, and for advance in psychiatry.

As stated in the Foreword by the late Dr. Alan Gregg, "The new insights which are developed in this book should be explored by every student of medicine." C. Z.

Basic Nutrition. By E. W. McHenry, M.A., Ph.D., Professor of Public Health and Nutrition, University of Toronto. Pp. 389; 31 ills. Philadelphia: J. B. Lippincott Company, 1957. Price, $5.00.

This text is informative and interesting. The material has been expertly selected to cover the essential aspects of nutrition for those unfamiliar with the clinical and experimental areas of this biologic science.

Classical concepts derived from earlier work and from present research are clearly delineated with respect to energy requirements and production, metabolism and utilization of foods, and nutritional investigation. The accessory nutrient factors, minerals and vitamins, receive ample attention with descriptions of their individual activities in the body economy. Both the Canadian and the United States dietary standards are described. The inclusion of discussions of special diets for use in various clinical states and of some basic principles of dietetics and food technology in a text prepared for the undergraduate student is commendable. Methods for appraisal of nutritional status of individuals and a discussion of public health aspects of malnutrition comprise the final chapters of the book. The engaging style and clarity of expression make the reading enjoyable as well as profitable in the study of nutrition.

C. S.

Drug Resistance of Microorganisms. By Robert J. Schnitzer and Emanuel Grunberg, Department of Chemotherapy, Hoffmann-LaRoche, Inc. Pp. 395; 31 ills. New York: Academic Press, Inc., 1957. Price, $10.00.

For the first time, the extensive literature on drug resistance of microorganisms has been gathered together and organized in book form. This is no small achievement, but it is not likely to be rewarded by wide recognition for the topic is a narrow one.

The subject matter divides itself quite sharply into four parts: (1) drug resistance among protozoa and spirochetes; (2) drug resistance of bacteria; (3) mechanism of drug resistance; (4) phenomena related to drug resistance. The literature coverage appears to be complete and accurate. Having assembled all this information, the authors proceed to put together a clear description of present knowledge, aided considerably by careful selection of tabular and illustrative material. The publisher is to be congratulated for the good quality of the printing and binding.

Certain limitations, however, should also be mentioned. For one thing the title is overly ambitious. By inference the term "Microorganisms" includes fungi and viruses; yet neither of these classes of microbes received more than casual mention. And the clinician looking for therapeutic hints will be disappointed because this book deals almost entirely with laboratory experimentation.

For the investigator in this field one of the most useful features is the 31-page Index, both by author and by subject. E. S.

Advances in Protein Chemistry, Vol. XI. Edited by M. L. Anson, Kenneth Bailey and John T. Edsall. Pp. 665; illustrated. New York: Academic Press, Inc., 1956. Price, $12.00.

This is another volume of an excellent series which summarize progress in various

aspects of protein chemistry. The topics in this volume are "Protein Structure in Relation to Function and Biosynthesis," by C. B. Anfinsen and R. R. Redfield; "Hormones of the Anterior Pituitary Gland. Part I. Growth and the Adrenocorticotropic Hormones," by C. H. Li; "Column Chromatography of Peptides and Proteins," by S. Moore and W. H. Stein; "Countercurrent Distribution in Protein Chemistry," by P. von Tavel and R. Signer; "Complex Formation between Metallic Cations and Proteins, Peptides, and Amino Acids," by F. R. N. Gurd and P. E. Wilcox; and "Measurement and Interpretation of Diffusion Coefficients of Proteins," by L. J. Gosting.

Remarkable advances continue to be made in this as well as other major fields of chemistry. Biochemists and others interested in fundamental clinical investigation will find much of value in this volume. C. Z.

ADVANCES IN VIRUS RESEARCH, VOL. IV. Edited by KENNETH M. SMITH AND MAX A. LAUFFER. Pp. 340; illustrated. New York: Academic Press, Inc., 1957. Price, $8.00.

THIS volume, like its predecessors, consists of a series of especially written summaries of important progress in certain areas of virus research. The material presented in this volume includes: 1) Factors in Virus Evolution, by C. H. Andrewes; 2) Bacteriophages as Genetic and Biochemical Systems, by A. D. Hershey; 3) Attachment and Penetration of Cells by Viruses, by L. J. Tolmach; 4) Particle Counts and Infectivity Titrations for Animal Viruses, by A. Isaacs; 5) The Anatomy of the Tobacco Mosaic Virus, by N. W. Pirie; 6) Effects of Non-Ionizing Radiations on Viruses, by A. Kleczkowski; 7) Effects of Changing Temperature on Plant Virus Diseases, by B. Kassanis; 8) Mechanical Transmission of Plant Viruses, by C. E. Yarwood; and 9) The Nature of Serological Relationships among Influenza Viruses, by K. E. Jensen.

The discussions are directed to a basic level and are of particular interest to virologists, biochemists, and biophysicists. Several of the presentations, however, offer important information or concepts for workers in epidemiology, infectious diseases, genetics, and diagnosis by laboratory methods. C. Z.

THE HAPPY LIFE OF A DOCTOR. By ROGER I. LEE, M.D. Pp. 278; 15 ills. Boston: Little, Brown & Co., 1956. Price, $4.00.

OUT of a rich and many-sided experience in medical practice, teaching and research, in military service and medical organizations, and as a member of the Harvard Corporation, Dr. Lee has distilled ingredients that have made his life a happy one. (Therefore disappointments are barely hinted at, there is no bitterness or betrayed confidence, and he can even poke fun at his rheumatic affliction.) He chats about many aspects of medicine and the medical profession that are of common interest to his reader, be he physician or layman: for example, Medicine and Morals; Truth in Medicine; Doctors in Government and Politics; Doctors' Fees; Lay Self-medication; Exercise and Athletics; An Ordinary Doctor Looks at Mental Disturbances, Psychoanalysis, Shock Therapy, Lobotomy; Geriatrics; The Doctor and His Hobbies; The Advantages of being Fat. The style is light and humorous, never pontifical; it readily passes the acid test of being read aloud. This is a book that everyone will enjoy. It is a "must" for all physicians and medical students who should find the essence of their own happiness in the chapter: The Joy of being a Doctor Today. R. K.

FUNDAMENTALS OF CLINICAL NEUROPHYSIOLOGY. By PAUL O. CHATFIELD, M.D., Former Chief, Section of Clinical Neurophysiology, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Md. Pp. 392; 151 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $8.50.

THIS valuable book is based upon lectures prepared for freshman medical students at Harvard Medical School by the author. The autonomic nervous system and physiological psychology are intentionally excluded. It is basic in its approach and is founded on well-established noncontroversial findings. The material which is used proves to be extremely well chosen to illustrate the points intended. The illustrations and figures are good. Medical students should find it very valuable since it is written with this group in mind. M. O.

MASKED EPILEPSY. By HUGH R. E. WALLIS, M.D., M.R.C.P., D.C.H., Consultant Pediatrician, Bath Clinical Area Medical Officer, Kingswood School. Pp. 51. Edinburgh and London: E. & S. Livingstone, Ltd., 1956 (The Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $2.50.

THIS monograph is highly recommended reading. It serves to emphasize a side of the

disease which well deserves emphasis. As the author says in his Preface, the fact that epilepsy may consist of sensory manifestations alone had left no earlier imprint on his mind when he began to think of this.

Cyclical vomiting, headaches, abdominal pain, pyrexia, nightmares, sleep-walking and night and day terrors are all considered as manifestations of epilepsy responding to appropriate suppressive therapy. Incidentally, the most useful drug in the author's experience, an experience perhaps not paralleled in this country, is phenobarbital. The book is amply illustrated by case reports. They represent, the author feels, temporal lobe epilepsy.

S. G.

PNEUMOENCEPHALOGRAPHY. By E. GRAEME ROBERTSON, M.D., F.R.C.P., F.R.A.C.P., Honorary Neurologist, Royal Melbourne Hospital, Melbourne. Pp. 482; 209 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $14.50.

THIS textbook is the result of the author's 20-years' experience with neurological problems in private and hospital practice. He considers the anatomical, physical, and clinical aspects of pneumoencephalography and has oriented this volume to neurologists, neurosurgeons, radiologists and clinicians, particularly pediatricians, who may have to use or recommend encephalography for their diagnostic problems.

The textbook is profusely illustrated. Wherever possible an attempt is made with diagrams and some color plates to correlate the anatomical structures with the distribution and pattern of the air shadows on the roentgenogram.

The material is divided into 28 chapters. The author evaluates anatomical factors in the flow of gas, the reasons for success and failure of ventricular filling, and the means of overcoming initial failure of filling.

Regional encephalography of the various cisternae, cerebral ventricles, and the subarachnoid space is covered in separate chapters. A chapter is devoted to tomography. Basic encephalographic technique is carefully described, both in the text and by numerous illustrations and diagrams.

Chapters are devoted to the following clinical conditions: Atrophic lesions, vascular diseases, injuries to the head, infection, hydrocephalus, mental abnormalities. The value of encephalography in childhood is described in a thorough and compact chapter.

This book proves that in this age of cerebral angiography, that the pneumoencephalogram still offers a great deal in diagnosis. The author has made a contribution to the improvement of technique and the evaluation of the pneumoencephalogram. It is worthy reading for all interested in this subject and as a supplement to the many good treatises that have already been published on encephalography.

M. S.

HYPOTHALAMUS UND THALAMUS. By W. R. HESS, Zurich. Pp. 70; 201 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $8.60.

THIS book is an atlas in parallel columns of German and English. It is based entirely upon the cat. The experiments represented were conducted between 1924 and 1951 by the author. Figures are numerous, of good quality and show responses with corresponding histological lesions and points of stimulation. Results are grouped on a functional basis. Although the work of the author is alone included it is a good source for those concerned with the field.

M.O.

THE PHYSICIAN-WRITER'S BOOK: TRICKS OF THE TRADE OF MEDICAL WRITING. By RICHARD M. HEWITT, A.M., M.D., Mayo Clinic. Pp. 415; 37 ills. Philadelphia: W. B. Saunders Co. 1957. Price, $9.00.

HERE is the best collection of good advice for the physician with the itch to write which this Reviewer has encountered, and so well-written that he read it from cover to cover. The arrangement and set-up are excellent, so that the "inexperienced, inexpert, occasional physician author" can easily find what he needs, and there is so much material that even the experienced writer can profit from its rich stores. The book is fervently recommended by this Editor to every medical writer.

R. K.

NEW BOOKS

Annual Epidemiological and Vital Statistics, 1953. Pp. 571. Geneva: World Health Organization, 1956. Price, $10.00.

THE World Health Organization here presents the epidemiological, vital and health statistics for the various countries and territories of the world for the year 1953, the sixth annual volume of the kind. This series is a valuable storehouse of information on the progress of hygiene and the evaluation of the health situation throughout the world.

R. K.

Psychiatry in Theory and Practice. By Beulah C. Bosselman, M.D., Professor of Psychiatry, College of Medicine, University of Illinois. Pp. 150. Springfield, Ill.: Charles C Thomas, 1957. Price, $4.00.

The author has succeeded in presenting a clear and readable precis of the theory and practice of psychiatry. This book is an excellent introduction to the field for the beginning resident. It represents an eclectic attitude with adherence to the most widely accepted and common sense viewpoints. The over-simplification of complex material might tend to lull the reader into a false sense of knowledge since the book is more oriented to what the psychiatrist knows and scarcely mentions the vast areas where the psychiatrist works in the dark. M. B.

Tuberculosis Control: Plans for Intensified Inter-Country Action in Europe. WHO Technical Report Series No. 112. Pp. 14. Geneva: World Health Organization, 1956. Price, $.30.

This report summarizes the discussions of a study group of the World Health Organization to enable European countries to exchange views on tuberculosis control in the light of recent experience. R. K.

Diagnosis and Typing in Leptospirosis. Report of a Study Group. WHO Technical Report Series No. 113. Pp. 10. Geneva: World Health Organization, 1956. Price, $.30.

A laudable effort to lay the foundations for a standardization of techniques used in the diagnosis of leptospirosis and the typing of pathogenic strains of leptospirae. R. K.

Ciba Collection of Medical Illustrations, Vol. 3. Digestive System. Part III. Liver, Biliary Tract and Pancreas. Prepared by Frank H. Netter, M.D., and edited by Ernst Oppenheimer, M.D. Pp. 165; 133 ills. Summit, N. J.: Ciba Pharmaceutical Products, Inc., 1957. Price, $10.50.

A fine collection of color plates and descriptive text with full Bibliography on the anatomy, physiology and diseases of the liver, biliary tract and pancreas. R. K.

Die Schutzimpfung gegen Poliomyelitis. Proceedings 5th German Congress, May 23 to 27, 1956. Pp. 291; 6 ills. Marburg: N. G. Elwert, Universitäts- und Verlags-Buchhandlung, 1956.

A series of papers and reports presented at the Fifth German Congress for Medical Postgraduate Education held in Berlin in May, 1956, and dealing with the programs and results of vaccination against poliomyelitis as carried out in Germany, in Europe and in the United States and elsewhere. Those who read German will here find an excellent summary of this important subject. R. K.

Vegetable Oils in Nutrition. By Dorothy M. Rothmann, Ph.D. Pp. 70; 7 ills. New York: Corn Products Refining Company, 1957.

This is a brief resume of the current status of saturated and unsaturated fatty acids in human nutrition derived from the extensive literature which has accumulated on this subject. C. S.

The Training of Sanitary Engineers. By Milivoj Petrik, Ing., M.S. Pp. 151. Geneva: World Health Organization, 1956. Price, $4.00.

The development of a country can be fully successful only if accompanied by the development of environmental sanitation and this, in turn, depends upon the availability of trained personnel. Such personnel is in short supply in most places. This volume, therefore, provides a much needed summary of information on training facilities in the United States and Europe. R. K.

The Eye in General Practice. By C. R. S. Jackson, M.A., B.M., B.Ch. (Oxon.), Ophthalmic Surgeon, Royal Infirmary, Edinburgh. Pp. 148; 25 ills. including 21 in color. Edinburgh and London: E. & S. Livingstone, Ltd., 1957 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $5.00.

This is a small book, full of brief descriptions and nicely illustrated. It covers most of the common eye conditions that the general doctor will see. It will enable the man in general practice to answer many of the questions his patients will ask. The facts are presented as clearly as space permits. The reviewer noted some conflicts in classification and drug recommendations. These are not in error but exist due to differences in U.S. and British nomenclature. The book is a worthwhile contribution to Ophthalmology in General Practice. L. H.

Emergencies in General Practice. British Medical Journal. Pp. 470; illustrated. London: British Medical Association House, 1957. Price, 25 s.

This volume brings under one cover a series of articles published in the British Medical Journal in 1955 and 1956 under the heading "Emergencies in General Practice." Nearly sixty authors have contributed highly practical summaries of a wide range of emergencies that confront physicians, especially general practitioners. They have been grouped under major headings: Hemorrhage and Thrombosis, Cardiorespiratory Crises, Anesthesia and Hazards of Therapy, Acute Abdominal Cases, Obstetrics, Fits and Coma, Electrocution, Burns and Gassing, Poisons, Acute Psychiatric States, Special

and Minor Surgery. General pratctitioners should find it particularly useful. R. K.

Notes on Atomic Energy for Medical Officers. Royal Naval Medical School, Alverstoke, Hampshire, England, Pp. 169; 71 ills. New York: Philosophical Library, Inc., 1956. Price, $4.75.

This little handbook has been prepared by the staff of the British Royal Naval Medical School to provide medical officers with basic information on the effects of an atomic explosion, the dangers from radiological warfare, the treatment of radiation casualties and protection against radiation. The presentation is concise and clear. R. K.

NEW EDITIONS

World Directory of Medical Schools. 2nd ed. Pp. 314. Geneva: World Health Organization, 1957. Price, $5.00.

Extensile Exposure. By Arnold K. Henry, M.B., Dublin, M.Ch.(Hon.), Trinity College, Dublin, Emeritus Professor of Clinical Surgery, University of Egypt; Professor of Anatomy, Royal College of Surgeons, Ireland. 2nd ed. Pp. 320; 198 ills. Baltimore: The Williams & Wilkins Co., 1957. Price, $10.00.

This is a very brief and interesting book in which the material is presented in a very pleasing fashion but quite different from the method of presentation we are accustomed to in the United States. This book is essentially a description of surgical technique based on the author's experience but with reference to the experience of others. He covers such diverse subjects as Exposure of the Shoulder Joint and Upper Humerus to the Removal of Pulmonary Emboli. However, the book concerns chiefly Exposure in Extremities. The illustrations are very apt. The anatomical illustrations and descriptions are quite clear. In essence this is a book in which tissue planes and exposure of various areas of the body are described. R. T.

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